

Spectroscopy: Principles, Theory, Techniques and Applications

Biomolecular Structures and Dynamics

Contents

Articles

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Spectroscopy--An Introduction

Spectroscopy

Spectroscopy was originally the study of the interaction between radiation and matter as a function of wavelength (λ). Historically, spectroscopy referred to the use of visible light dispersed according to its wavelength, e.g. by a prism. Later the concept was expanded greatly to comprise any measurement of a quantity as a function of either wavelength or frequency. Thus, it also can refer to a response to an alternating field or varying frequency (ν). A further extension of the scope of the definition added energy (E) as a variable, once the very close relationship $E = h\nu$ for photons was realized (h is the Planck constant). A plot of the response as a function of wavelength—or more commonly frequency—is referred to as a spectrum; see also spectral linewidth.

Spectrometry is the spectroscopic technique used to assess the concentration or amount of a given chemical (atomic, molecular, or ionic) species. In this case, the instrument that performs such measurements is a spectrometer, spectrophotometer, or spectrograph.

Spectroscopy/spectrometry is often used in physical and analytical chemistry for the identification of substances through the spectrum emitted from or absorbed by them.

Spectroscopy/spectrometry is also heavily used in astronomy and remote sensing. Most large telescopes have spectrographs, which are used either to measure the chemical composition and physical properties of astronomical objects or to measure their velocities from the Doppler shift of their spectral lines.

Classification of methods

Nature of excitation measured

The type of spectroscopy depends on the physical quantity measured. Normally, the quantity that is measured is an intensity, of energy either absorbed or produced.

- Electromagnetic spectroscopy involves interactions of matter with electromagnetic radiation, such as light.
- Electron spectroscopy involves interactions with electron beams. Auger spectroscopy involves inducing the Auger effect with an electron beam. In this case the measurement typically involves the kinetic energy of the electron as variable.
- Acoustic spectroscopy involves the frequency of sound.
- Dielectric spectroscopy involves the frequency of an external electrical field
- Mechanical spectroscopy involves the frequency of an external mechanical stress, e.g. a torsion applied to a piece of material.

Measurement process

Most spectroscopic methods are differentiated as either atomic or molecular based on whether or not they apply to atoms or molecules. Along with that distinction, they can be classified on the nature of their interaction:

- Absorption spectroscopy uses the range of the electromagnetic spectra in which a substance absorbs. This includes atomic absorption spectroscopy and various molecular techniques, such as infrared, ultraviolet-visible and microwave spectroscopy.
 - Emission spectroscopy uses the range of electromagnetic spectra in which a substance radiates (emits). The substance first must absorb energy. This energy can be from a variety of sources, which determines the name of
-

the subsequent emission, like luminescence. Molecular luminescence techniques include spectrofluorimetry.

- Scattering spectroscopy measures the amount of light that a substance scatters at certain wavelengths, incident angles, and polarization angles. One of the most useful applications of light scattering spectroscopy is Raman spectroscopy.

Common types

Absorption

Absorption spectroscopy is a technique in which the power of a beam of light measured before and after interaction with a sample is compared. Specific absorption techniques tend to be referred to by the wavelength of radiation measured such as ultraviolet, infrared or microwave absorption spectroscopy. Absorption occurs when the energy of the photons matches the energy difference between two states of the material.

Fluorescence

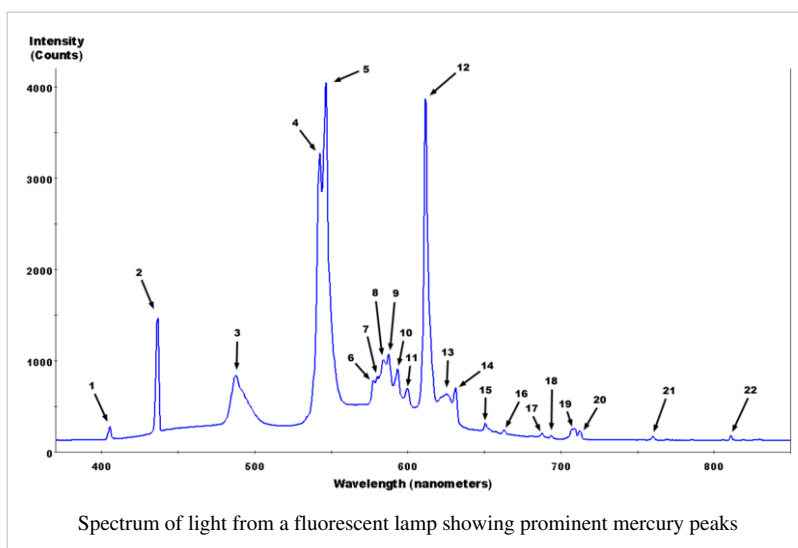
Fluorescence spectroscopy uses higher energy photons to excite a sample, which will then emit lower energy photons. This technique has become popular for its biochemical and medical applications, and can be used for confocal microscopy, fluorescence resonance energy transfer, and fluorescence lifetime imaging.

X-ray

When X-rays of sufficient frequency (energy) interact with a substance, inner shell electrons in the atom are

excited to outer empty orbitals, or they may be removed completely, ionizing the atom. The inner shell "hole" will then be filled by electrons from outer orbitals. The energy available in this de-excitation process is emitted as radiation (fluorescence) or will remove other less-bound electrons from the atom (Auger effect). The absorption or emission frequencies (energies) are characteristic of the specific atom. In addition, for a specific atom, small frequency (energy) variations that are characteristic of the chemical bonding occur. With a suitable apparatus, these characteristic X-ray frequencies or Auger electron energies can be measured. X-ray absorption and emission spectroscopy is used in chemistry and material sciences to determine elemental composition and chemical bonding.

X-ray crystallography is a scattering process; crystalline materials scatter X-rays at well-defined angles. If the wavelength of the incident X-rays is known, this allows calculation of the distances between planes of atoms within the crystal. The intensities of the scattered X-rays give information about the atomic positions and allow the arrangement of the atoms within the crystal structure to be calculated.



Flame technique

Liquid solution samples are aspirated into a burner or nebulizer/burner combination, desolvated, atomized, and sometimes excited to a higher energy electronic state. The use of a flame during analysis requires fuel and oxidant, typically in the form of gases. Common fuel gases used are acetylene (ethyne) or hydrogen. Common oxidant gases used are oxygen, air, or nitrous oxide. These methods are often capable of analyzing metallic element analytes in the part per million, billion, or possibly lower concentration ranges. Light detectors are needed to detect light with the analysis information coming from the flame.

- **Atomic emission spectroscopy** - This method uses flame excitation; atoms are excited from the heat of the flame to emit light. This method commonly uses a total consumption burner with a round burning outlet. A higher temperature flame than atomic absorption spectroscopy (AA) is typically used to produce excitation of analyte atoms. Since analyte atoms are excited by the heat of the flame, no special elemental lamps to shine into the flame are needed. A high resolution polychromator can be used to produce an emission intensity vs. wavelength spectrum over a range of wavelengths showing multiple element excitation lines, meaning multiple elements can be detected in one run. Alternatively, a monochromator can be set at one wavelength to concentrate on analysis of a single element at a certain emission line. Plasma emission spectroscopy is a more modern version of this method. See Flame emission spectroscopy for more details.
- **Atomic absorption spectroscopy** (often called AA) - This method commonly uses a pre-burner nebulizer (or nebulizing chamber) to create a sample mist and a slot-shaped burner that gives a longer pathlength flame. The temperature of the flame is low enough that the flame itself does not excite sample atoms from their ground state. The nebulizer and flame are used to desolvate and atomize the sample, but the excitation of the analyte atoms is done by the use of lamps shining through the flame at various wavelengths for each type of analyte. In AA, the amount of light absorbed after going through the flame determines the amount of analyte in the sample. A graphite furnace for heating the sample to desolvate and atomize is commonly used for greater sensitivity. The graphite furnace method can also analyze some solid or slurry samples. Because of its good sensitivity and selectivity, it is still a commonly used method of analysis for certain trace elements in aqueous (and other liquid) samples.
- **Atomic fluorescence spectroscopy** - This method commonly uses a burner with a round burning outlet. The flame is used to solvate and atomize the sample, but a lamp shines light at a specific wavelength into the flame to excite the analyte atoms in the flame. The atoms of certain elements can then fluoresce emitting light in a different direction. The intensity of this fluorescing light is used for quantifying the amount of analyte element in the sample. A graphite furnace can also be used for atomic fluorescence spectroscopy. This method is not as commonly used as atomic absorption or plasma emission spectroscopy.
- **Plasma emission spectroscopy** - In some ways similar to flame atomic emission spectroscopy, it has largely replaced it.
 - A direct-current plasma (DCP) is created by an electrical discharge between two electrodes. A plasma support gas is necessary, and Ar is common. Samples can be deposited on one of the electrodes, or if conducting can make up one electrode.
- Glow discharge-optical emission spectrometry (GD-OES)
- Inductively coupled plasma-atomic emission spectrometry (ICP-AES)
- Laser Induced Breakdown Spectroscopy (LIBS) (LIBS), also called Laser-induced plasma spectrometry (LIPS)
- Microwave-induced plasma (MIP)
- **Spark or arc (emission) spectroscopy** is used for the analysis of metallic elements in solid samples. For non-conductive materials, a sample is ground with graphite powder to make it conductive. In traditional arc spectroscopy methods, a sample of the solid was commonly ground up and destroyed during analysis. An electric arc or spark is passed through the sample, heating the sample to a high temperature to excite the atoms in it. The

excited analyte atoms glow, emitting light at various wavelengths that could be detected by common spectroscopic methods. Since the conditions producing the arc emission typically are not controlled quantitatively, the analysis for the elements is qualitative. Nowadays, the spark sources with controlled discharges under an argon atmosphere allow that this method can be considered eminently quantitative, and its use is widely expanded worldwide through production control laboratories of foundries and steel mills.

Visible

Many atoms emit or absorb visible light. In order to obtain a fine line spectrum, the atoms must be in a gas phase. This means that the substance has to be vaporised. The spectrum is studied in absorption or emission. Visible absorption spectroscopy is often combined with UV absorption spectroscopy in UV/Vis spectroscopy. Although this form may be uncommon as the human eye is a similar indicator, it still proves useful when distinguishing colours.

Ultraviolet

All atoms absorb in the Ultraviolet (UV) region because these photons are energetic enough to excite outer electrons. If the frequency is high enough, photoionization takes place. UV spectroscopy is also used in quantifying protein and DNA concentration as well as the ratio of protein to DNA concentration in a solution. Several amino acids usually found in protein, such as tryptophan, absorb light in the 280 nm range and DNA absorbs light in the 260 nm range. For this reason, the ratio of 260/280 nm absorbance is a good general indicator of the relative purity of a solution in terms of these two macromolecules. Reasonable estimates of protein or DNA concentration can also be made this way using Beer's law.

Infrared

Infrared spectroscopy offers the possibility to measure different types of inter atomic bond vibrations at different frequencies. Especially in organic chemistry the analysis of IR absorption spectra shows what type of bonds are present in the sample. It is also an important method for analysing polymers and constituents like fillers, pigments and plasticizers.

Near Infrared (NIR)

The near infrared NIR range, immediately beyond the visible wavelength range, is especially important for practical applications because of the much greater penetration depth of NIR radiation into the sample than in the case of mid IR spectroscopy range. This allows also large samples to be measured in each scan by NIR spectroscopy, and is currently employed for many practical applications such as: rapid grain analysis, medical diagnosis pharmaceuticals/medicines,^[1] biotechnology, genomics analysis, proteomic analysis, interactomics research, inline textile monitoring, food analysis and chemical imaging/hyperspectral imaging of intact organisms,^{[2] [3] [4]} plastics, textiles, insect detection, forensic lab application, crime detection and various military applications. Interpretation of Near-Infrared Spectra is important for chemical identification.^[5]

Raman

Raman spectroscopy uses the inelastic scattering of light to analyse vibrational and rotational modes of molecules. The resulting 'fingerprints' are an aid to analysis.

Coherent anti-Stokes Raman spectroscopy (CARS)

CARS is a recent technique that has high sensitivity and powerful applications for *in vivo* spectroscopy and imaging.^[6]

Nuclear magnetic resonance

Nuclear magnetic resonance spectroscopy analyzes the magnetic properties of certain atomic nuclei to determine different electronic local environments of hydrogen, carbon, or other atoms in an organic compound or other compound. This is used to help determine the structure of the compound.

Mössbauer

Transmission or conversion-electron (CEMS) modes of Mössbauer spectroscopy probe the properties of specific isotope nuclei in different atomic environments by analyzing the resonant absorption of characteristic energy gamma-rays known as the Mössbauer effect.

Other types

There are many different types of materials analysis techniques under the broad heading of "spectroscopy", utilizing a wide variety of different approaches to probing material properties, such as absorbance, reflection, emission, scattering, thermal conductivity, and refractive index.

- Acoustic spectroscopy
 - Auger spectroscopy is a method used to study surfaces of materials on a micro-scale. It is often used in connection with electron microscopy.
 - Cavity ring down spectroscopy
 - Circular Dichroism spectroscopy
 - Deep-level transient spectroscopy measures concentration and analyzes parameters of electrically active defects in semiconducting materials
 - Dielectric spectroscopy
 - Dual polarisation interferometry measures the real and imaginary components of the complex refractive index
 - Force spectroscopy
 - Fourier transform spectroscopy is an efficient method for processing spectra data obtained using interferometers. Nearly all infrared spectroscopy techniques (such as FTIR) and nuclear magnetic resonance (NMR) are based on Fourier transforms.
 - Fourier transform infrared spectroscopy (FTIR)
 - Hadron spectroscopy studies the energy/mass spectrum of hadrons according to spin, parity, and other particle properties. Baryon spectroscopy and meson spectroscopy are both types of hadron spectroscopy.
 - Inelastic electron tunneling spectroscopy (IETS) uses the changes in current due to inelastic electron-vibration interaction at specific energies that can also measure optically forbidden transitions.
 - Inelastic neutron scattering is similar to Raman spectroscopy, but uses neutrons instead of photons.
 - Laser spectroscopy uses tunable lasers^[7] and other types of coherent emission sources, such as optical parametric oscillators,^[8] for selective excitation of atomic or molecular species.
 - Ultra fast laser spectroscopy
-

- Mechanical spectroscopy involves interactions with macroscopic vibrations, such as phonons. An example is acoustic spectroscopy, involving sound waves.
- Neutron spin echo spectroscopy measures internal dynamics in proteins and other soft matter systems
- Nuclear magnetic resonance (NMR)
- Photoacoustic spectroscopy measures the sound waves produced upon the absorption of radiation.
- Photothermal spectroscopy measures heat evolved upon absorption of radiation.
- Raman optical activity spectroscopy exploits Raman scattering and optical activity effects to reveal detailed information on chiral centers in molecules.
- Terahertz spectroscopy uses wavelengths above infrared spectroscopy and below microwave or millimeter wave measurements.
- Time-resolved spectroscopy is the spectroscopy of matter in situations where the properties are changing with time.
- Thermal infrared spectroscopy measures thermal radiation emitted from materials and surfaces and is used to determine the type of bonds present in a sample as well as their lattice environment. The techniques are widely used by organic chemists, mineralogists, and planetary scientists.

Background subtraction

Background subtraction is a term typically used in spectroscopy when one explains the process of acquiring a background radiation level (or ambient radiation level) and then makes an algorithmic adjustment to the data to obtain qualitative information about any deviations from the background, even when they are an order of magnitude less decipherable than the background itself.

Background subtraction can affect a number of statistical calculations (Continuum, Compton, Bremsstrahlung) leading to improved overall system performance.

Applications

- Estimate weathered wood exposure times using Near infrared spectroscopy.^[9]
- Cure monitoring of composites using Optical fibers

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- [8] F. J. Duarte (Ed.), *Tunable Laser Applications*, 2nd Ed. (CRC, 2009) Chapter 2. (<http://www.opticsjournal.com/tla.htm>)
- [9] "Using NIR Spectroscopy to Predict Weathered Wood Exposure Times" (http://www.fpl.fs.fed.us/documnts/pdf2006/fpl_2006_wang002.pdf). .

External links

- Spectroscopy links (<http://www.dmoz.org//Science/Physics/Optics/Spectroscopy//>) at the Open Directory Project
- Amateur spectroscopy links (<http://www.dmoz.org//Science/Astronomy/Amateur/Spectroscopy//>) at the Open Directory Project
- Timeline of Spectroscopy (<http://spectroscopyonline.findanalytichem.com/spectroscopy/article/articleDetail.jsp?id=381944&sk=&date=&pageID=8>)
- Chemometric Analysis for Spectroscopy (<http://www.laboratoryequipment.com/article-chemometric-analysis-for-spectroscopy.aspx>)
- The Science of Spectroscopy (<http://www.scienceofspectroscopy.info>) - supported by NASA, includes OpenSpectrum, a Wiki-based learning tool for spectroscopy that anyone can edit
- A Short Study of the Characteristics of two Lab Spectroscopes (<http://ioannis.virtualcomposer2000.com/spectroscope/>)
- NIST government spectroscopy data (<http://physics.nist.gov/Pubs/AtSpec/index.html>)
- Potentiodynamic Electrochemical Impedance Spectroscopy (<http://www.abc.chemistry.bsu.by/vi/>)

Fourier transform spectroscopy

Fourier transform spectroscopy is a measurement technique whereby spectra are collected based on measurements of the coherence of a radiative source, using time-domain or space-domain measurements of the electromagnetic radiation or other type of radiation. It can be applied to a variety of types of spectroscopy including optical spectroscopy, infrared spectroscopy (FTIR, FT-NIRS), nuclear magnetic resonance (NMR) and magnetic resonance spectroscopic imaging (MRSI)^[1], mass spectrometry and electron spin resonance spectroscopy. There are several methods for measuring the temporal coherence of the light (see: field-autocorrelation), including the continuous wave *Michelson* or *Fourier transform* spectrometer and the pulsed Fourier transform spectrograph (which is more sensitive and has a much shorter sampling time than conventional spectroscopic techniques, but is only applicable in a laboratory environment).

The term *Fourier transform spectroscopy* reflects the fact that in all these techniques, a Fourier transform is required to turn the raw data into the actual spectrum, and in many of the cases in optics involving interferometers, is based on the Wiener–Khinchin theorem.

Conceptual introduction

Measuring an emission spectrum

One of the most basic tasks in spectroscopy is to characterize the spectrum of a light source: How much light is emitted at each different wavelength. The most straightforward way to measure a spectrum is to pass the light through a monochromator, an instrument that blocks all of the light *except* the light at a certain wavelength (the un-blocked wavelength is set by a knob on the monochromator). Then the intensity of this remaining (single-wavelength) light is measured. The measured intensity directly indicates how much light is emitted at that wavelength. By varying the monochromator's wavelength setting, the full spectrum can be measured. This simple scheme in fact describes how *some* spectrometers work.

Fourier transform spectroscopy is a less intuitive way to get the same information. Rather than allowing only one wavelength at a time to pass through to the detector, this technique lets through a beam containing many different wavelengths of light at once, and measures the *total* beam intensity. Next, the beam is modified to contain a *different* combination of wavelengths, giving a second data point. This process is repeated many times. Afterwards, a computer takes all this data and works backwards to infer how much light there is at each wavelength.

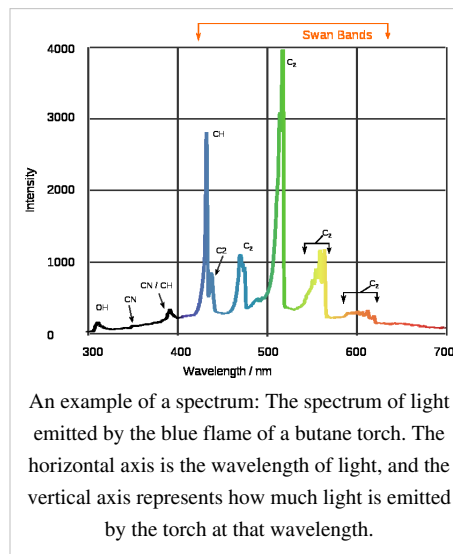
To be more specific, between the light source and the detector, there is a certain configuration of mirrors that allows some wavelengths to pass through but blocks others (due to wave interference). The beam is modified for each new data point by moving one of the mirrors; this changes the set of wavelengths that can pass through.

As mentioned, computer processing is required to turn the raw data (light intensity for each mirror position) into the desired result (light intensity for each wavelength). The processing required turns out to be a common algorithm called the Fourier transform (hence the name, "Fourier transform spectroscopy"). The raw data is sometimes called an "interferogram".

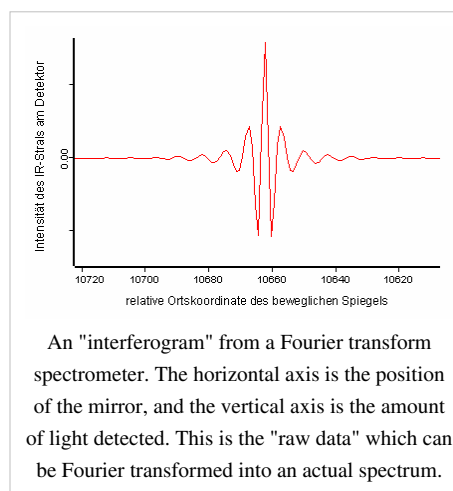
Measuring an absorption spectrum

The method of Fourier transform spectroscopy can also be used for absorption spectroscopy. The primary example is "FTIR Spectroscopy", a common technique in chemistry.

In general, the goal of absorption spectroscopy is to measure how well a sample absorbs or transmits light at each different wavelength. Although absorption spectroscopy and emission spectroscopy are different in principle, they are closely related in practice; any technique for emission spectroscopy can also be used for absorption spectroscopy. First, the emission spectrum of a broadband lamp is measured (this is called the "background spectrum"). Second, the emission spectrum of the same lamp *shining through the sample* is measured (this is called the "sample spectrum"). The sample will absorb some of the light, causing the spectra to be different. The ratio of the "sample spectrum" to the "background spectrum" is directly related to the sample's absorption spectrum.



An example of a spectrum: The spectrum of light emitted by the blue flame of a butane torch. The horizontal axis is the wavelength of light, and the vertical axis represents how much light is emitted by the torch at that wavelength.

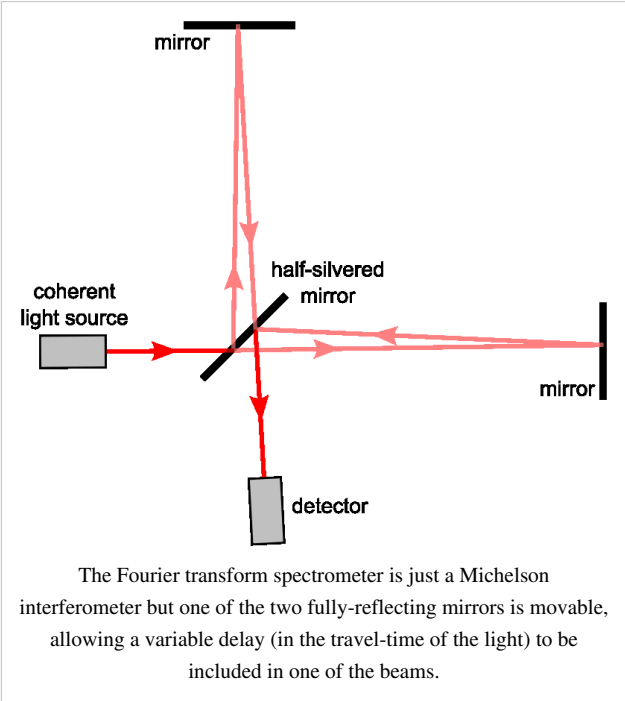


An "interferogram" from a Fourier transform spectrometer. The horizontal axis is the position of the mirror, and the vertical axis is the amount of light detected. This is the "raw data" which can be Fourier transformed into an actual spectrum.

Accordingly, the technique of "Fourier transform spectroscopy" can be used both for measuring emission spectra (for example, the emission spectrum of a star), *and* absorption spectra (for example, the absorption spectrum of a glass of liquid).

Continuous wave *Michelson* or *Fourier transform* spectrograph

The Michelson spectrograph is similar to the instrument used in the Michelson-Morley experiment. Light from the source is split into two beams by a half-silvered mirror, one is reflected off a fixed mirror and one off a moving mirror which introduces a time delay—the Fourier transform spectrometer is just a Michelson interferometer with a movable mirror. The beams interfere, allowing the temporal coherence of the light to be measured at each different time delay setting, effectively converting the time domain into a spatial coordinate. By making measurements of the signal at many discrete positions of the moving mirror, the spectrum can be reconstructed using a Fourier transform of the temporal coherence of the light. Michelson spectrographs are capable of very high spectral resolution observations of very bright sources. The Michelson or Fourier transform spectrograph was popular for infra-red applications at a time when infra-red astronomy only had single pixel detectors. Imaging Michelson spectrometers are a possibility, but in general have been supplanted by imaging Fabry–Pérot instruments which are easier to construct.



Extracting the spectrum

The intensity as a function of the path length difference in the interferometer p and wavenumber $\tilde{\nu} = 1/\lambda$ is ^[2]

$$I(p, \tilde{\nu}) = I(\tilde{\nu})[1 + \cos(2\pi\tilde{\nu}p)],$$

where $I(\tilde{\nu})$ is the spectrum to be determined. Note that it is not necessary for $I(\tilde{\nu})$ to be modulated by the sample before the interferometer. In fact, most FTIR spectrometers place the sample after the interferometer in the optical path. The total intensity at the detector is

$$I(p) = \int_0^\infty I(p, \tilde{\nu}) d\tilde{\nu} = \int_0^\infty I(\tilde{\nu})[1 + \cos(2\pi\tilde{\nu}p)] d\tilde{\nu}.$$

This is just a Fourier cosine transform. The inverse gives us our desired result in terms of the measured quantity $I(p)$:

$$I(\tilde{\nu}) = 4 \int_0^\infty [I(p) - \frac{1}{2}I(p=0)] \cos(2\pi\tilde{\nu}p) dp.$$

Pulsed *Fourier transform* spectrometer

A pulsed *Fourier transform* spectrometer does not employ transmittance techniques. In the most general description of pulsed FT spectrometry, a sample is exposed to an energizing event which causes a periodic response. The frequency of the periodic response, as governed by the field conditions in the spectrometer, is indicative of the measured properties of the analyte.

Examples of pulsed Fourier transform spectrometry

In magnetic spectroscopy (EPR, NMR), an RF pulse in a strong ambient magnetic field is used as the energizing event. This turns the magnetic particles at an angle to the ambient field, resulting in gyration. The gyrating spins then induce a periodic current in a detector coil. Each spin exhibits a characteristic frequency of gyration (relative to the field strength) which reveals information about the analyte.

In Fourier transform mass spectrometry, the energizing event is the injection of the charged sample into the strong electromagnetic field of a cyclotron. These particles travel in circles, inducing a current in a fixed coil on one point in their circle. Each traveling particle exhibits a characteristic cyclotron frequency-field ratio revealing the masses in the sample.

Free induction decay

Pulsed FT spectrometry gives the advantage of requiring a single, time-dependent measurement which can easily deconvolute a set of similar but distinct signals. The resulting composite signal, is called a *free induction decay*, because typically the signal will decay due to inhomogeneities in sample frequency, or simply unrecoverable loss of signal due to entropic loss of the property being measured.

Stationary forms of Fourier transform spectrometers

In addition to the scanning forms of Fourier transform spectrometers, there are a number of stationary or self-scanned forms.^[3] While the analysis of the interferometric output is similar to that of the typical scanning interferometer, significant differences apply, as shown in the published analyses. Some stationary forms retain the Fellgett multiplex advantage, and their use in the spectral region where detector noise limits apply is similar to the scanning forms of the FTS. In the photon-noise limited region, the application of stationary interferometers is dictated by specific consideration for the spectral region and the application.

Fellgett advantage

One of the most important advantages of Fourier transform spectroscopy was shown by P.B. Fellgett, an early advocate of the method. The Fellgett advantage, also known as the multiplex principle, states that when obtaining a spectrum when measurement noise is dominated by detector noise, a multiplex spectrometer such as a Fourier transform spectrometer will produce a relative improvement in signal-to-noise ratio, compared to an equivalent scanning monochromator, of the order of the square root of m , where m is the number of sample points comprising the spectrum.

Converting spectra from time domain to frequency domain

$$S(t) = \int_{-\infty}^{\infty} I(\nu) e^{-i\nu 2\pi t} d\nu$$

The sum is performed over all contributing frequencies to give a signal $S(t)$ in the time domain.

$$I(\nu) = \int_{-\infty}^{\infty} S(t) e^{i\nu 2\pi t} dt$$

gives non-zero value when $S(t)$ contains a component that matches the oscillating function.

Remember that

$$e^{ix} = \cos x + i \sin x$$

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External links

- Description of how a Fourier transform spectrometer works (<http://scienceworld.wolfram.com/physics/FourierTransformSpectrometer.html>)
- The Michelson or Fourier transform spectrograph (<http://www.astro.livjm.ac.uk/courses/phys362/notes/>)
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- Fourier Transform Spectroscopy Topical Meeting and Tabletop Exhibit (<http://www.osa.org/meetings/topicalmeetings/fts/default.aspx>)

Spectroscopy Theory

Quantum mechanics

Quantum mechanics, also known as **quantum physics** or **quantum theory**, is a branch of physics providing a mathematical description of much of the dual particle-like and wave-like behavior and interactions of energy and matter. It departs from classical mechanics primarily at the atomic and subatomic scales, the so-called quantum realm. In advanced topics of quantum mechanics, some of these behaviors are macroscopic and only emerge at very low or very high energies or temperatures. The name, coined by Max Planck, derives from the observation that some physical quantities can be changed only by discrete amounts, or quanta, as multiples of the Planck constant, rather than being capable of varying continuously or by any arbitrary amount. For example, the angular momentum, or more generally the action, of an electron bound into an atom or molecule is quantized. While an unbound electron does not exhibit quantized energy levels, an electron bound in an atomic orbital has quantized values of angular momentum. In the context of quantum mechanics, the wave-particle duality of energy and matter and the uncertainty principle provide a unified view of the behavior of photons, electrons and other atomic-scale objects.

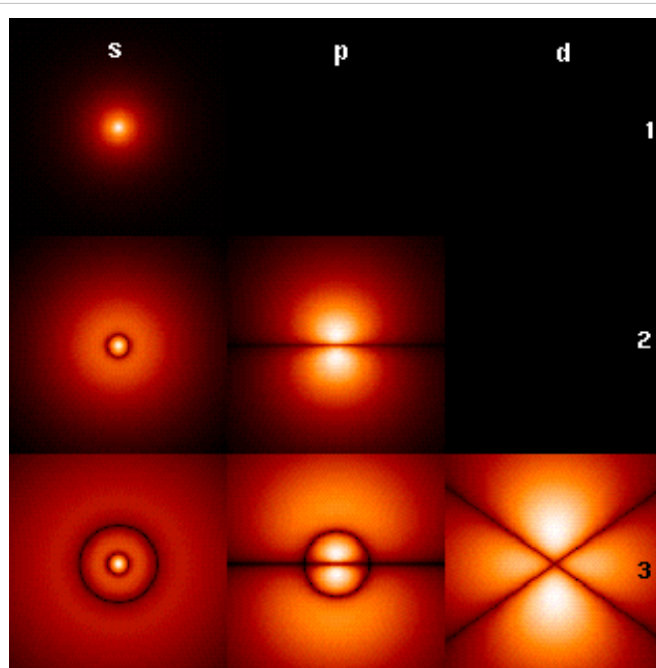


Fig. 1: Probability densities corresponding to the wavefunctions of an electron in a hydrogen atom possessing definite energy levels (increasing from the top of the image to the bottom: $n = 1, 2, 3, \dots$) and angular momentum (increasing across from left to right: $s, p, d, \dots$). Brighter areas correspond to higher probability density in a position measurement. Wavefunctions like these are directly comparable to Chladni's figures of acoustic modes of vibration in classical physics and are indeed modes of oscillation as well: they possess a sharp energy and thus a keen frequency. The angular momentum and energy are quantized, and only take on discrete values like those shown (as is the case for resonant frequencies in acoustics).

The mathematical formulations of quantum mechanics are abstract. Similarly, the implications are often non-intuitive in terms of classic physics. The centerpiece of the mathematical system is the wavefunction. The wavefunction is a mathematical function providing information about the probability amplitude of position and momentum of a particle. Mathematical manipulations of the wavefunction usually involve the bra-ket notation, which requires an understanding of complex numbers and linear functionals. The wavefunction treats the object as a quantum harmonic oscillator and the mathematics is akin to that of acoustic resonance. Many of the results of quantum mechanics do not have models that are easily visualized in terms of classical mechanics; for instance, the ground state in the quantum mechanical model is a non-zero energy state that is the lowest permitted energy state of a system, rather than a more traditional system that is thought of as simply being at rest with zero kinetic energy.

Historically, the earliest versions of quantum mechanics were formulated in the first decade of the 20th century at around the same time as the atomic theory and the corpuscular theory of light as updated by Einstein first came to be widely accepted as scientific fact; these latter theories can be viewed as quantum theories of matter and

electromagnetic radiation. Quantum theory was significantly reformulated in the mid-1920s away from the old quantum theory towards the quantum mechanics formulated by Werner Heisenberg, Max Born, Wolfgang Pauli and their associates, accompanied by the acceptance of the Copenhagen interpretation of Niels Bohr. By 1930, quantum mechanics had been further unified and formalized by the work of Paul Dirac and John von Neumann, with a greater emphasis placed on measurement in quantum mechanics, the statistical nature of our knowledge of reality and philosophical speculation about the role of the observer. Quantum mechanics has since branched out into almost every aspect of 20th century physics and other disciplines such as quantum chemistry, quantum electronics, quantum optics and quantum information science. Much 19th century physics has been re-evaluated as the classical limit of quantum mechanics, and its more advanced developments in terms of quantum field theory, string theory, and speculative quantum gravity theories.

History

The history of quantum mechanics dates back to the 1838 discovery of cathode rays by Michael Faraday. This was followed by the 1859 statement of the black body radiation problem by Gustav Kirchhoff, the 1877 suggestion by Ludwig Boltzmann that the energy states of a physical system can be discrete, and the 1900 quantum hypothesis of Max Planck.^[1] Planck's hypothesis that energy is radiated and absorbed in discrete "quanta", or "energy elements", enabled the correct derivation of the observed patterns of black body radiation. According to Planck, each energy element E is proportional to its frequency ν :

$$E = h\nu$$

where h is Planck's action constant. Planck cautiously insisted that this was simply an aspect of the processes of absorption and emission of radiation and had nothing to do with the physical reality of the radiation itself.^[2] However, in 1905 Albert Einstein interpreted Planck's quantum hypothesis realistically and used it to explain the photoelectric effect, in which shining light on certain materials can eject electrons from the material. Einstein postulated that light itself consists of individual quanta of energy, later called photons.^[3]

The foundations of quantum mechanics were established during the first half of the twentieth century by Niels Bohr, Werner Heisenberg, Max Planck, Louis de Broglie, Albert Einstein, Erwin Schrödinger, Max Born, John von Neumann, Paul Dirac, Wolfgang Pauli, David Hilbert, and others. In the mid-1920s, developments in quantum mechanics quickly led to its becoming the standard formulation for atomic physics. In the summer of 1925, Bohr and Heisenberg published results that closed the "Old Quantum Theory". Out of deference to their dual state as particles, light quanta came to be called photons (1926). From Einstein's simple postulation was born a flurry of debating, theorizing and testing. Thus, the entire field of quantum physics emerged leading to its wider acceptance at the Fifth Solvay Conference in 1927.

The other exemplar that led to quantum mechanics was the study of electromagnetic waves such as light. When it was found in 1900 by Max Planck that the energy of waves could be described as consisting of small packets or quanta, Albert Einstein further developed this idea to show that an electromagnetic wave such as light could be described by a particle called the photon with a discrete energy dependent on its frequency. This led to a theory of unity between subatomic particles and electromagnetic waves called wave–particle duality in which particles and waves were neither one nor the other, but had certain properties of both. While quantum mechanics describes the world of the very small, it also is needed to explain certain macroscopic quantum systems such as superconductors and superfluids.

The word *quantum* derives from Latin meaning "how great" or "how much".^[4] In quantum mechanics, it refers to a discrete unit that quantum theory assigns to certain physical quantities, such as the energy of an atom at rest (see Figure 1). The discovery that particles are discrete packets of energy with wave-like properties led to the branch of physics that deals with atomic and subatomic systems which is today called quantum mechanics. It is the underlying mathematical framework of many fields of physics and chemistry, including condensed matter physics, solid-state physics, atomic physics, molecular physics, computational physics, computational chemistry, quantum chemistry,

particle physics, nuclear chemistry, and nuclear physics.^[5] Some fundamental aspects of the theory are still actively studied.^[6] Quantum mechanics is essential to understand the behavior of systems at atomic length scales and smaller. For example, if classical mechanics governed the workings of an atom, electrons would rapidly travel towards and collide with the nucleus, making stable atoms impossible. However, in the natural world the electrons normally remain in an uncertain, non-deterministic "smeared" (wave–particle wave function) orbital path around or through the nucleus, defying classical electromagnetism.^[7] Quantum mechanics was initially developed to provide a better explanation of the atom, especially the spectra of light emitted by different atomic species. The quantum theory of the atom was developed as an explanation for the electron's staying in its orbital, which could not be explained by Newton's laws of motion and by Maxwell's laws of classical electromagnetism. Broadly speaking, quantum mechanics incorporates four classes of phenomena for which classical physics cannot account:

- The quantization (discretization) of certain physical quantities
- wave–particle duality
- uncertainty principle
- quantum entanglement

Mathematical formulations

In the mathematically rigorous formulation of quantum mechanics developed by Paul Dirac^[8] and John von Neumann,^[9] the possible states of a quantum mechanical system are represented by unit vectors (called "state vectors"). Formally, these reside in a complex separable Hilbert space (variously called the "state space" or the "associated Hilbert space" of the system) well defined up to a complex number of norm 1 (the phase factor). In other words, the possible states are points in the projectivization of a Hilbert space, usually called the complex projective space. The exact nature of this Hilbert space is dependent on the system; for example, the state space for position and momentum states is the space of square-integrable functions, while the state space for the spin of a single proton is just the product of two complex planes. Each observable is represented by a maximally Hermitian (precisely: by a self-adjoint) linear operator acting on the state space. Each eigenstate of an observable corresponds to an eigenvector of the operator, and the associated eigenvalue corresponds to the value of the observable in that eigenstate. If the operator's spectrum is discrete, the observable can only attain those discrete eigenvalues.

In the formalism of quantum mechanics, the state of a system at a given time is described by a complex wave function, also referred to as state vector in a complex vector space.^[10] This abstract mathematical object allows for the calculation of probabilities of outcomes of concrete experiments. For example, it allows one to compute the probability of finding an electron in a particular region around the nucleus at a particular time. Contrary to classical mechanics, one can never make simultaneous predictions of conjugate variables, such as position and momentum, with accuracy. For instance, electrons may be considered to be located somewhere within a region of space, but with their exact positions being unknown. Contours of constant probability, often referred to as "clouds", may be drawn around the nucleus of an atom to conceptualize where the electron might be located with the most probability. Heisenberg's uncertainty principle quantifies the inability to precisely locate the particle given its conjugate momentum.^[11]

As the result of a measurement, the wave function containing the probability information for a system collapses from a given initial state to a particular eigenstate of the observable. The possible results of a measurement are the eigenvalues of the operator representing the observable — which explains the choice of *Hermitian* operators, for which all the eigenvalues are real. We can find the probability distribution of an observable in a given state by computing the spectral decomposition of the corresponding operator. Heisenberg's uncertainty principle is represented by the statement that the operators corresponding to certain observables do not commute.

The probabilistic nature of quantum mechanics thus stems from the act of measurement. This is one of the most difficult aspects of quantum systems to understand. It was the central topic in the famous Bohr-Einstein debates, in which the two scientists attempted to clarify these fundamental principles by way of thought experiments. In the

decades after the formulation of quantum mechanics, the question of what constitutes a "measurement" has been extensively studied. Interpretations of quantum mechanics have been formulated to do away with the concept of "wavefunction collapse"; see, for example, the relative state interpretation. The basic idea is that when a quantum system interacts with a measuring apparatus, their respective wavefunctions become entangled, so that the original quantum system ceases to exist as an independent entity. For details, see the article on measurement in quantum mechanics.^[12] Generally, quantum mechanics does not assign definite values to observables. Instead, it makes predictions using probability distributions; that is, the probability of obtaining possible outcomes from measuring an observable. Often these results are skewed by many causes, such as dense probability clouds^[13] or quantum state nuclear attraction.^{[14] [15]} Naturally, these probabilities will depend on the quantum state at the "instant" of the measurement. Hence, uncertainty is involved in the value. There are, however, certain states that are associated with a definite value of a particular observable. These are known as eigenstates of the observable ("eigen" can be translated from German as inherent or as a characteristic).^[16]

In the everyday world, it is natural and intuitive to think of everything (every observable) as being in an eigenstate. Everything appears to have a definite position, a definite momentum, a definite energy, and a definite time of occurrence. However, quantum mechanics does not pinpoint the exact values of a particle for its position and momentum (since they are conjugate pairs) or its energy and time (since they too are conjugate pairs); rather, it only provides a range of probabilities of where that particle might be given its momentum and momentum probability. Therefore, it is helpful to use different words to describe states having *uncertain* values and states having *definite* values (eigenstate). Usually, a system will not be in an eigenstate of the observable we are interested in. However, if one measures the observable, the wavefunction will instantaneously be an eigenstate (or generalized eigenstate) of that observable. This process is known as wavefunction collapse, a debatable process.^[17] It involves expanding the system under study to include the measurement device. If one knows the corresponding wave function at the instant before the measurement, one will be able to compute the probability of collapsing into each of the possible eigenstates. For example, the free particle in the previous example will usually have a wavefunction that is a wave packet centered around some mean position x_0 , neither an eigenstate of position nor of momentum. When one measures the position of the particle, it is impossible to predict with certainty the result.^[12] It is probable, but not certain, that it will be near x_0 , where the amplitude of the wave function is large. After the measurement is performed, having obtained some result x , the wave function collapses into a position eigenstate centered at x .^[18]

The time evolution of a quantum state is described by the Schrödinger equation, in which the Hamiltonian, the operator corresponding to the total energy of the system, generates time evolution. The time evolution of wave functions is deterministic in the sense that, given a wavefunction at an initial time, it makes a definite prediction of what the wavefunction will be at any later time.^[19]

During a measurement, on the other hand, the change of the wavefunction into another one is not deterministic, but rather unpredictable, i.e., random. A time-evolution simulation can be seen here.^{[20] [21]} Wave functions can change as time progresses. An equation known as the Schrödinger equation describes how wave functions change in time, a role similar to Newton's second law in classical mechanics. The Schrödinger equation, applied to the aforementioned example of the free particle, predicts that the center of a wave packet will move through space at a constant velocity, like a classical particle with no forces acting on it. However, the wave packet will also spread out as time progresses, which means that the position becomes more uncertain. This also has the effect of turning position eigenstates (which can be thought of as infinitely sharp wave packets) into broadened wave packets that are no longer position eigenstates.^[22]

Some wave functions produce probability distributions that are constant, or independent of time, such as when in a stationary state of constant energy, time drops out of the absolute square of the wave function. Many systems that are treated dynamically in classical mechanics are described by such "static" wave functions. For example, a single electron in an unexcited atom is pictured classically as a particle moving in a circular trajectory around the atomic nucleus, whereas in quantum mechanics it is described by a static, spherically symmetric wavefunction surrounding

the nucleus (Fig. 1). (Note that only the lowest angular momentum states, labeled s , are spherically symmetric).^[23]

The Schrödinger equation acts on the entire probability amplitude, not merely its absolute value. Whereas the absolute value of the probability amplitude encodes information about probabilities, its phase encodes information about the interference between quantum states. This gives rise to the wave-like behavior of quantum states. It turns out that analytic solutions of Schrödinger's equation are only available for a small number of model Hamiltonians, of which the quantum harmonic oscillator, the particle in a box, the hydrogen molecular ion and the hydrogen atom are the most important representatives. Even the helium atom, which contains just one more electron than hydrogen, defies all attempts at a fully analytic treatment. There exist several techniques for generating approximate solutions. For instance, in the method known as perturbation theory one uses the analytic results for a simple quantum mechanical model to generate results for a more complicated model related to the simple model by, for example, the addition of a weak potential energy. Another method is the "semi-classical equation of motion" approach, which applies to systems for which quantum mechanics produces weak deviations from classical behavior. The deviations can be calculated based on the classical motion. This approach is important for the field of quantum chaos.

There are numerous mathematically equivalent formulations of quantum mechanics. One of the oldest and most commonly used formulations is the transformation theory proposed by Cambridge theoretical physicist Paul Dirac, which unifies and generalizes the two earliest formulations of quantum mechanics, matrix mechanics (invented by Werner Heisenberg)^{[24] [25]} and wave mechanics (invented by Erwin Schrödinger).^[26] In this formulation, the instantaneous state of a quantum system encodes the probabilities of its measurable properties, or "observables". Examples of observables include energy, position, momentum, and angular momentum. Observables can be either continuous (e.g., the position of a particle) or discrete (e.g., the energy of an electron bound to a hydrogen atom).^[27] An alternative formulation of quantum mechanics is Feynman's path integral formulation, in which a quantum-mechanical amplitude is considered as a sum over histories between initial and final states; this is the quantum-mechanical counterpart of action principles in classical mechanics.

Interactions with other scientific theories

The fundamental rules of quantum mechanics are very deep. They assert that the state space of a system is a Hilbert space and the observables are Hermitian operators acting on that space, but do not tell us which Hilbert space or which operators, or if it even exists. These must be chosen appropriately in order to obtain a quantitative description of a quantum system. An important guide for making these choices is the correspondence principle, which states that the predictions of quantum mechanics reduce to those of classical physics when a system moves to higher energies or equivalently, larger quantum numbers. In other words, classical mechanics is simply a quantum mechanics of large systems. This "high energy" limit is known as the *classical* or *correspondence limit*. One can therefore start from an established classical model of a particular system, and attempt to guess the underlying quantum model that gives rise to the classical model in the correspondence limit.

When quantum mechanics was originally formulated, it was applied to models whose correspondence limit was non-relativistic classical mechanics. For instance, the well-known model of the quantum harmonic oscillator uses an explicitly non-relativistic expression for the kinetic energy of the oscillator, and is thus a quantum version of the classical harmonic oscillator.

Early attempts to merge quantum mechanics with special relativity involved the replacement of the Schrödinger equation with a covariant equation such as the Klein-Gordon equation or the Dirac equation. While these theories were successful in explaining many experimental results, they had certain unsatisfactory qualities stemming from their neglect of the relativistic creation and annihilation of particles. A fully relativistic quantum theory required the development of quantum field theory, which applies quantization to a field rather than a fixed set of particles. The first complete quantum field theory, quantum electrodynamics, provides a fully quantum description of the electromagnetic interaction. The full apparatus of quantum field theory is often unnecessary for describing electrodynamic systems. A simpler approach, one employed since the inception of quantum mechanics, is to treat

charged particles as quantum mechanical objects being acted on by a classical electromagnetic field. For example, the elementary quantum model of the hydrogen atom describes the electric field of the hydrogen atom using a classical $-\frac{e^2}{4\pi\epsilon_0 r}$ Coulomb potential. This "semi-classical" approach fails if quantum fluctuations in the electromagnetic field play an important role, such as in the emission of photons by charged particles. Quantum field theories for the strong nuclear force and the weak nuclear force have been developed. The quantum field theory of the strong nuclear force is called quantum chromodynamics, and describes the interactions of the subnuclear particles: quarks and gluons. The weak nuclear force and the electromagnetic force were unified, in their quantized forms, into a single quantum field theory known as electroweak theory, by the physicists Abdus Salam, Sheldon Glashow and Steven Weinberg. These three men shared the Nobel Prize in Physics in 1979 for this work.^[28]

It has proven difficult to construct quantum models of gravity, the remaining fundamental force. Semi-classical approximations are workable, and have led to predictions such as Hawking radiation. However, the formulation of a complete theory of quantum gravity is hindered by apparent incompatibilities between general relativity, the most accurate theory of gravity currently known, and some of the fundamental assumptions of quantum theory. The resolution of these incompatibilities is an area of active research, and theories such as string theory are among the possible candidates for a future theory of quantum gravity. Classical mechanics has been extended into the complex domain and complex classical mechanics exhibits behaviours similar to quantum mechanics.^[29]

Quantum mechanics and classical physics

Predictions of quantum mechanics have been verified experimentally to a very high degree of accuracy. According to the correspondence principle between classical and quantum mechanics, all objects obey the laws of quantum mechanics, and classical mechanics is just an approximation for large systems (or a statistical quantum mechanics of a large collection of particles). The laws of classical mechanics thus follow from the laws of quantum mechanics as a statistical average at the limit of large systems or large quantum numbers.^[30] However, chaotic systems do not have good quantum numbers, and quantum chaos studies the relationship between classical and quantum descriptions in these systems.

Quantum coherence is an essential difference between classical and quantum theories, and is illustrated by the Einstein-Podolsky-Rosen paradox. Quantum interference involves the addition of *probability amplitudes*, whereas when classical waves interfere there is an addition of *intensities*. For microscopic bodies, the extension of the system is much smaller than the coherence length, which gives rise to long-range entanglement and other nonlocal phenomena characteristic of quantum systems.^[31] Quantum coherence is not typically evident at macroscopic scales, although an exception to this rule can occur at extremely low temperatures, when quantum behavior can manifest itself on more macroscopic scales (see Bose-Einstein condensate). This is in accordance with the following observations:

- Many macroscopic properties of a classical system are a direct consequences of the quantum behavior of its parts. For example, the stability of bulk matter (which consists of atoms and molecules which would quickly collapse under electric forces alone), the rigidity of solids, and the mechanical, thermal, chemical, optical and magnetic properties of matter are all results of the interaction of electric charges under the rules of quantum mechanics.^[32]
- While the seemingly exotic behavior of matter posited by quantum mechanics and relativity theory become more apparent when dealing with extremely fast-moving or extremely tiny particles, the laws of classical Newtonian physics remain accurate in predicting the behavior of large objects—of the order of the size of large molecules and bigger—at velocities much smaller than the velocity of light.^[33]

Relativity and quantum mechanics

Main articles: Quantum gravity and Theory of everything

Even with the defining postulates of both Einstein's theory of general relativity and quantum theory being indisputably supported by rigorous and repeated empirical evidence and while they do not directly contradict each other theoretically (at least with regard to primary claims), they are resistant to being incorporated within one cohesive model.^[34]

Einstein himself is well known for rejecting some of the claims of quantum mechanics. While clearly contributing to the field, he did not accept the more philosophical consequences and interpretations of quantum mechanics, such as the lack of deterministic causality and the assertion that a single subatomic particle can occupy numerous areas of space at one time. He also was the first to notice some of the apparently exotic consequences of entanglement and used them to formulate the Einstein-Podolsky-Rosen paradox, in the hope of showing that quantum mechanics had unacceptable implications. This was 1935, but in 1964 it was shown by John Bell (see Bell inequality) that, although Einstein was correct in identifying seemingly paradoxical implications of quantum mechanical nonlocality, these implications could be experimentally tested. Alain Aspect's initial experiments in 1982, and many subsequent experiments since, have verified quantum entanglement.

According to the paper of J. Bell and the Copenhagen interpretation (the common interpretation of quantum mechanics by physicists since 1927), and contrary to Einstein's ideas, quantum mechanics was not at the same time

- a "realistic" theory
- and a *local* theory.

The Einstein-Podolsky-Rosen paradox shows in any case that there exist experiments by which one can measure the state of one particle and instantaneously change the state of its entangled partner, although the two particles can be an arbitrary distance apart; however, this effect does not violate causality, since no transfer of information happens. Quantum entanglement is at the basis of quantum cryptography, with high-security commercial applications in banking and government.

Gravity is negligible in many areas of particle physics, so that unification between general relativity and quantum mechanics is not an urgent issue in those applications. However, the lack of a correct theory of quantum gravity is an important issue in cosmology and physicists' search for an elegant "theory of everything". Thus, resolving the inconsistencies between both theories has been a major goal of twentieth- and twenty-first-century physics. Many prominent physicists, including Stephen Hawking, have labored in the attempt to discover a theory underlying *everything*, combining not only different models of subatomic physics, but also deriving the universe's four forces—the strong force, electromagnetism, weak force, and gravity—from a single force or phenomenon. One of the leaders in this field is Edward Witten, a theoretical physicist who formulated the groundbreaking M-theory, which is an attempt at describing the supersymmetrical based string theory.

Attempts at a unified field theory

As of 2010 the quest for unifying the fundamental forces through quantum mechanics is still ongoing. Quantum electrodynamics (or "quantum electromagnetism"), which is currently (in the perturbative regime at least) the most accurately tested physical theory,^[35] has been successfully merged with the weak nuclear force into the electroweak force and work is currently being done to merge the electroweak and strong force into the electrostrong force. Current predictions state that at around 10^{14} GeV the three aforementioned forces are fused into a single unified field,^[36] Beyond this "grand unification," it is speculated that it may be possible to merge gravity with the other three gauge symmetries, expected to occur at roughly 10^{19} GeV. However—and while special relativity is parsimoniously incorporated into quantum electrodynamics—the expanded general relativity, currently the best theory describing the gravitation force, has not been fully incorporated into quantum theory.

Philosophical implications

Since its inception, the many counter-intuitive results of quantum mechanics have provoked strong philosophical debate and many interpretations. Even fundamental issues such as Max Born's basic rules concerning probability amplitudes and probability distributions took decades to be appreciated.

Richard Feynman said, "I think I can safely say that nobody understands quantum mechanics."^[37]

The Copenhagen interpretation, due largely to the Danish theoretical physicist Niels Bohr, is the interpretation of the quantum mechanical formalism most widely accepted amongst physicists. According to it, the probabilistic nature of quantum mechanics is not a temporary feature which will eventually be replaced by a deterministic theory, but instead must be considered to be a final renunciation of the classical ideal of causality. In this interpretation, it is believed that any well-defined application of the quantum mechanical formalism must always make reference to the experimental arrangement, due to the complementarity nature of evidence obtained under different experimental situations.

Albert Einstein, himself one of the founders of quantum theory, disliked this loss of determinism in measurement. (This dislike is the source of his famous quote, "God does not play dice with the universe.") Einstein held that there should be a local hidden variable theory underlying quantum mechanics and that, consequently, the present theory was incomplete. He produced a series of objections to the theory, the most famous of which has become known as the Einstein-Podolsky-Rosen paradox. John Bell showed that the EPR paradox led to experimentally testable differences between quantum mechanics and local realistic theories. Experiments have been performed confirming the accuracy of quantum mechanics, thus demonstrating that the physical world cannot be described by local realistic theories.^[38] The *Bohr-Einstein debates* provide a vibrant critique of the Copenhagen Interpretation from an epistemological point of view.

The Everett many-worlds interpretation, formulated in 1956, holds that all the possibilities described by quantum theory simultaneously occur in a multiverse composed of mostly independent parallel universes.^[39] This is not accomplished by introducing some new axiom to quantum mechanics, but on the contrary by *removing* the axiom of the collapse of the wave packet: All the possible consistent states of the measured system and the measuring apparatus (including the observer) are present in a *real* physical (not just formally mathematical, as in other interpretations) quantum superposition. Such a superposition of consistent state combinations of different systems is called an entangled state. While the multiverse is deterministic, we perceive non-deterministic behavior governed by probabilities, because we can observe only the universe, i.e. the consistent state contribution to the mentioned superposition, we inhabit. Everett's interpretation is perfectly consistent with John Bell's experiments and makes them intuitively understandable. However, according to the theory of quantum decoherence, the parallel universes will never be accessible to us. This inaccessibility can be understood as follows: Once a measurement is done, the measured system becomes entangled with both the physicist who measured it and a huge number of other particles, some of which are photons flying away towards the other end of the universe; in order to prove that the wave function did not collapse one would have to bring all these particles back and measure them again, together with the system that was measured originally. This is completely impractical, but even if one could theoretically do this, it would destroy any evidence that the original measurement took place (including the physicist's memory).

Applications

Quantum mechanics had enormous success in explaining many of the features of our world. The individual behaviour of the subatomic particles that make up all forms of matter—electrons, protons, neutrons, photons and others—can often only be satisfactorily described using quantum mechanics. Quantum mechanics has strongly influenced string theory, a candidate for a theory of everything (see reductionism) and the multiverse hypothesis.

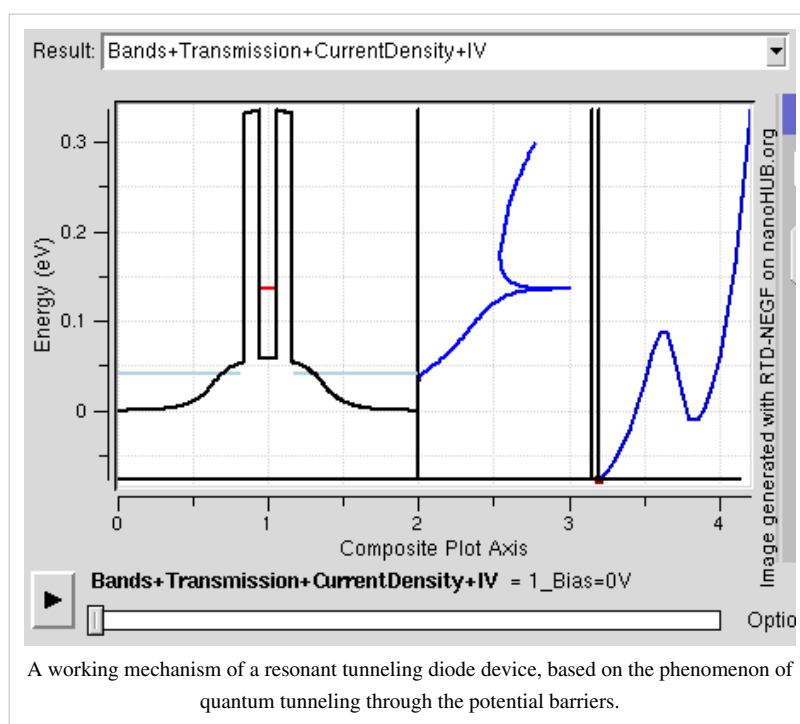
Quantum mechanics is important for understanding how individual atoms combine covalently to form chemicals or molecules. The application of quantum mechanics to chemistry is known as quantum chemistry. (Relativistic) quantum mechanics can in principle mathematically describe most of chemistry. Quantum mechanics can provide quantitative insight into ionic and covalent bonding processes by explicitly showing which molecules are energetically favorable to which others, and by approximately how much.^[40] Most of the calculations performed in computational chemistry rely on quantum mechanics.^[41]

Much of modern technology operates at a scale where quantum effects are significant. Examples include the laser, the transistor (and thus the microchip), the electron microscope, and magnetic resonance imaging. The study of semiconductors led to the invention of the diode and the transistor, which are indispensable for modern electronics.

Researchers are currently seeking robust methods of directly manipulating quantum states. Efforts are being made to develop quantum cryptography, which will allow guaranteed secure transmission of information. A more distant goal is the development of quantum computers, which are expected to perform certain computational tasks exponentially faster than classical computers. Another active research topic is quantum teleportation, which deals with techniques to transmit quantum information over arbitrary distances.

Quantum tunneling is vital in many devices, even in the simple light switch, as otherwise the electrons in the electric current could not penetrate the potential barrier made up of a layer of oxide. Flash memory chips found in USB drives use quantum tunneling to erase their memory cells.

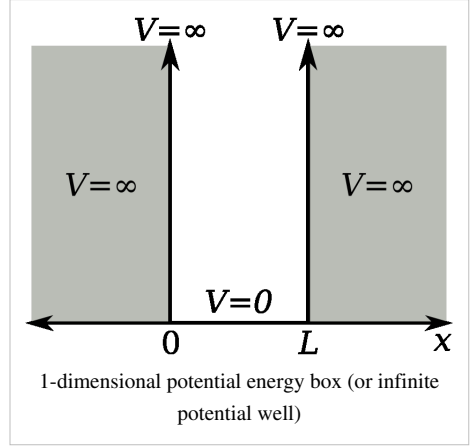
Quantum mechanics primarily applies to the atomic regimes of matter and energy, but some systems exhibit quantum mechanical effects on a large scale; superfluidity (the frictionless flow of a liquid at temperatures near absolute zero) is one well-known example. Quantum theory also provides accurate descriptions for many previously unexplained phenomena such as black body radiation and the stability of electron orbitals. It has also given insight into the workings of many different biological systems, including smell receptors and protein structures.^[42] Recent work on photosynthesis has provided evidence that quantum correlations play an essential role in this most fundamental process of the plant kingdom.^[43] Even so, classical physics often can be a good approximation to results otherwise obtained by **quantum physics**, typically in circumstances with large numbers of particles or large quantum numbers. (However, some open questions remain in the field of quantum chaos.)



Examples

Particle in a box

The particle in a 1-dimensional potential energy box is the most simple example where restraints lead to the quantization of energy levels. The box is defined as having zero potential energy inside a certain region and infinite potential energy everywhere outside that region. For the 1-dimensional case in the x direction, the time-independent Schrödinger equation can be written as:^[44]



$$-\frac{\hbar^2}{2m} \frac{d^2\psi}{dx^2} = E\psi.$$

Writing the differential operator

$$\hat{p}_x = -i\hbar \frac{d}{dx}$$

the previous equation can be seen to be evocative of the classic analogue

$$\frac{1}{2m} \hat{p}_x^2 = E$$

with E as the energy for the state ψ , in this case coinciding with the kinetic energy of the particle.

The general solutions of the Schrödinger equation for the particle in a box are:

$$\psi(x) = Ae^{ikx} + Be^{-ikx} \quad E = \frac{\hbar^2 k^2}{2m}$$

or, from Euler's formula,

$$\psi(x) = C \sin kx + D \cos kx.$$

The presence of the walls of the box determines the values of C , D , and k . At each wall ($x = 0$ and $x = L$), $\psi = 0$.

Thus when $x = 0$,

$$\psi(0) = 0 = C \sin 0 + D \cos 0 = D$$

and so $D = 0$. When $x = L$,

$$\psi(L) = 0 = C \sin kL.$$

C cannot be zero, since this would conflict with the Born interpretation. Therefore $\sin kL = 0$, and so it must be that kL is an integer multiple of π . Therefore,

$$k = \frac{n\pi}{L} \quad n = 1, 2, 3, \dots$$

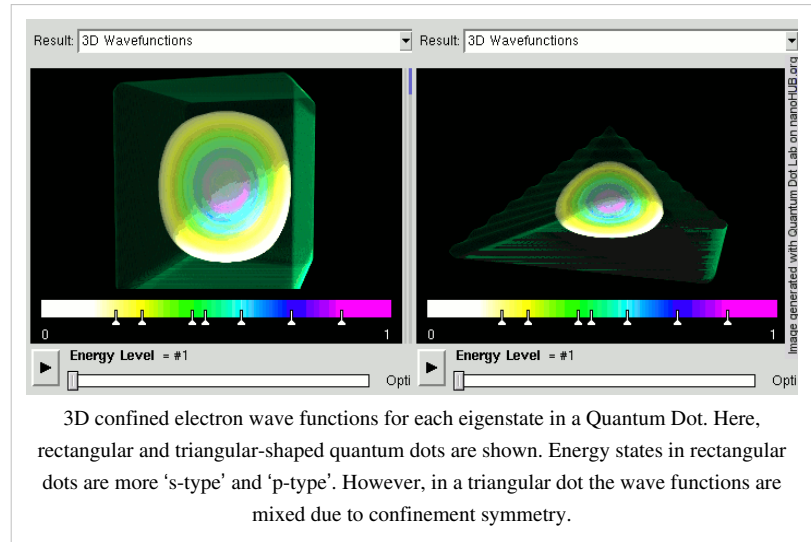
The quantization of energy levels follows from this constraint on k , since

$$E = \frac{\hbar^2 \pi^2 n^2}{2mL^2} = \frac{n^2 h^2}{8mL^2}.$$

Free particle

For example, consider a free particle. In quantum mechanics, there is wave-particle duality so the properties of the particle can be described as the properties of a wave. Therefore, its quantum state can be represented as a wave of arbitrary shape and extending over space as a wave function. The position and momentum of the particle are observables. The Uncertainty Principle states that both the position and the momentum cannot simultaneously be measured with full precision at the same time. However, one can measure the position alone of a

moving free particle creating an eigenstate of position with a wavefunction that is very large (a Dirac delta) at a particular position x and zero everywhere else. If one performs a position measurement on such a wavefunction, the result x will be obtained with 100% probability (full certainty). This is called an eigenstate of position (mathematically more precise: a *generalized position eigenstate (eigendistribution)*). If the particle is in an eigenstate of position then its momentum is completely unknown. On the other hand, if the particle is in an eigenstate of momentum then its position is completely unknown.^[45] In an eigenstate of momentum having a plane wave form, it can be shown that the wavelength is equal to h/p , where h is Planck's constant and p is the momentum of the eigenstate.^[46]



Notes

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Course material

- Doron Cohen: Lecture notes in Quantum Mechanics (comprehensive, with advanced topics). (<http://arxiv.org/abs/quant-ph/0605180>)
- MIT OpenCourseWare: Chemistry (<http://ocw.mit.edu/OcwWeb/Chemistry/index.htm>).
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- Motion Mountain, Volume IV (<http://www.motionmountain.net/download.html>) - A modern introduction to quantum theory, with several animations.
- AQME (<http://www.nanohub.org/topics/AQME>) : Advancing Quantum Mechanics for Engineers — by T.Barzso, D.Vasileska and G.Klimeck online learning resource with simulation tools on nanohub
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- Online course on *Quantum Transport* (<http://nanohub.org/resources/2039>)

FAQs

- Many-worlds or relative-state interpretation. (<http://www.hedweb.com/manworld.htm>)
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Media

- Lectures on Quantum Mechanics by Leonard Susskind (http://www.youtube.com/view_play_list?p=84C10A9CB1D13841)
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Quantum field theory

Quantum field theory (QFT)^[1] provides a theoretical framework for constructing quantum mechanical models of systems classically parametrized (represented) by an infinite number of dynamical degrees of freedom, that is, fields and (in a condensed matter context) many-body systems. It is the natural and quantitative language of particle physics and condensed matter physics. Most theories in modern particle physics, including the Standard Model of elementary particles and their interactions, are formulated as relativistic quantum field theories. Quantum field theories are used in many contexts, elementary particle physics being the most vital example, where the particle count/number going into a reaction fluctuates and changes, differing from the count/number going out, for example, and for the description of critical phenomena and quantum phase transitions, such as in the BCS theory of superconductivity, also see phase transition, quantum phase transition, critical phenomena. Quantum field theory is thought by many to be the unique and correct outcome of combining the rules of quantum mechanics with special relativity.

In perturbative quantum field theory, the forces between particles are mediated by other particles. The electromagnetic force between two electrons is caused by an exchange of photons. Intermediate vector bosons mediate the weak force and gluons mediate the strong force. There is currently no complete quantum theory of the remaining fundamental force, gravity, but many of the proposed theories postulate the existence of a graviton particle that mediates it. These force-carrying particles are virtual particles and, by definition, cannot be detected while carrying the force, because such detection will imply that the force is not being carried. In addition, the notion of "force mediating particle" comes from perturbation theory, and thus does not make sense in a context of bound states.

In QFT photons are not thought of as 'little billiard balls', they are considered to be field quanta - necessarily chunked ripples in a field, or "excitations," that 'look like' particles. Fermions, like the electron, can also be described

as ripples/excitations in a field, where each kind of fermion has its own field. In summary, the classical visualisation of "everything is particles and fields," in quantum field theory, resolves into "everything is particles," which then resolves into "everything is fields." In the end, particles are regarded as excited states of a field (field quanta). The gravitational field and the electromagnetic field are the only two fundamental fields in Nature that have infinite range and a corresponding classical low-energy limit, which greatly diminishes and hides their "particle-like" excitations. Albert Einstein, in 1905, attributed "particle-like" and discrete exchanges of momenta and energy, characteristic of "field quanta," to the electromagnetic field. Originally, his principal motivation was to explain the thermodynamics of radiation. Although it is often claimed that the photoelectric and Compton effects require a quantum description of the EM field, this is now understood to be untrue, and proper proof of the quantum nature of radiation is now taken up into modern quantum optics as in the antibunching effect^[2]. The word "photon" was coined in 1926 by the great physical chemist Gilbert Newton Lewis (see also the articles photon antibunching and laser).

The "low-energy limit" of the correct quantum field-theoretic description of the electromagnetic field, quantum electrodynamics, is believed to become James Clerk Maxwell's 1864 theory, although the "classical limit" of quantum electrodynamics has not been as widely explored as that of quantum mechanics. Presumably, the as yet unknown correct quantum field-theoretic treatment of the gravitational field will become and "look exactly like" Einstein's general theory of relativity in the "low-energy limit." Indeed, quantum field theory itself is quite possibly the low-energy-effective-field-theory limit of a more fundamental theory such as superstring theory. Compare in this context the article effective field theory.

History

Quantum field theory originated in the 1920s from the problem of creating a quantum mechanical theory of the electromagnetic field. In 1925 Werner Heisenberg, Max Born, and Pascual Jordan constructed such a theory by expressing the field's internal degrees of freedom as an infinite set of harmonic oscillators and by employing the usual procedure for quantizing those oscillators. This theory assumed that no electric charges or currents were present, and today would be called a free field theory. The first reasonably complete theory of quantum electrodynamics, which included both the electromagnetic field and electrically charged matter (specifically, electrons) as quantum mechanical objects, was created by Paul Dirac in 1927.^[3] This quantum field theory could be used to model important processes such as the emission of a photon by an electron dropping into a quantum state of lower energy, a process in which the *number of particles changes* — one atom in the initial state becomes an atom plus a photon in the final state. It is now understood that the ability to describe such processes is one of the most important features of quantum field theory.

It was evident from the beginning that a proper quantum treatment of the electromagnetic field had to somehow incorporate Einstein's relativity theory, which had after all grown out of the study of classical electromagnetism. This need to *put together relativity and quantum mechanics* was the second major motivation in the development of quantum field theory. Pascual Jordan and Wolfgang Pauli showed in 1928 that quantum fields could be made to behave in the way predicted by special relativity during coordinate transformations (specifically, they showed that the field commutators were Lorentz invariant). A further boost for quantum field theory came with the discovery of the Dirac equation, which was originally formulated and interpreted as a single-particle equation analogous to the Schrödinger equation, but unlike the Schrödinger equation, the Dirac equation satisfies both Lorentz invariance, that is, the requirements of special relativity, and the rules of quantum mechanics. The Dirac equation accommodated the spin-1/2 value of the electron and accounted for its magnetic moment as well as giving accurate predictions for the spectra of hydrogen. The attempted interpretation of the Dirac equation as a single-particle equation could not be maintained long, however, and finally it was shown that several of its undesirable properties (such as negative-energy states) could be made sense of by reformulating and reinterpreting the Dirac equation as a true field equation, in this case for the quantized "Dirac field" or the "electron field", with the "negative-energy solutions" pointing to the existence of anti-particles. This work was performed first by Dirac himself with the invention of hole

theory 1930 and also by Wendell Furry, Robert Oppenheimer, Vladimir Fock, and others. Schrödinger, during the same period that he discovered his famous equation in 1926, also independently found the relativistic generalization of it known as the Klein-Gordon equation but dismissed it since, without spin, it predicted impossible properties for the hydrogen spectrum. See Oskar Klein, Walter Gordon. All relativistic wave equations that describe spin-zero particles are said to be of the Klein-Gordon type.

A subtle and careful analysis in 1933 and later in 1950 by Niels Bohr and Leon Rosenfeld showed that there is a fundamental limitation on the ability to simultaneously measure the electric and magnetic field strengths that enter into the description of charges in interaction with radiation, imposed by the uncertainty principle, which must apply to all canonically conjugate quantities. This limitation is crucial for the successful formulation and interpretation of a quantum field theory of photons and electrons (quantum electrodynamics), and indeed, any perturbative quantum field theory. The analysis of Bohr and Rosenfeld explains fluctuations in the values of the electromagnetic field that differ from the classically "allowed" values distant from the sources of the field. Their analysis was crucial to showing that the limitations and physical implications of the uncertainty principle apply to all dynamical systems, whether fields or material particles. Their analysis also convinced most people that any notion of returning to a fundamental description of nature based on classical field theory, such as what Einstein aimed at with his numerous and failed attempts at a classical unified field theory, was simply out of the question.

The third thread in the development of quantum field theory was the need to *handle the statistics of many-particle systems* consistently and with ease. In 1927 Jordan tried to extend the canonical quantization of fields to the many-body wave functions of identical particles, a procedure that is sometimes called second quantization. In 1928, Jordan and Eugene Wigner found that the quantum field describing electrons, or other fermions, had to be expanded using anti-commuting creation and annihilation operators due to the Pauli exclusion principle. This thread of development was incorporated into many-body theory and strongly influenced condensed matter physics and nuclear physics.

Despite its early successes quantum field theory was plagued by several serious theoretical difficulties. Basic physical quantities, such as the self-energy of the electron, the energy shift of electron states due to the presence of the electromagnetic field, gave infinite, divergent contributions — a nonsensical result — when computed using the perturbative techniques available in the 1930s and most of the 1940s. The electron self-energy problem was already a serious issue in the classical electromagnetic field theory, where the attempt to attribute to the electron a finite size or extent (the classical electron-radius) led immediately to the question of what non-electromagnetic stresses would need to be invoked, which would presumably hold the electron together against the Coulomb repulsion of its finite-sized "parts". The situation was dire, and had certain features that reminded many of the "Rayleigh-Jeans difficulty". What made the situation in the 1940s so desperate and gloomy, however, was the fact that the correct ingredients (the second-quantized Maxwell-Dirac field equations) for the theoretical description of interacting photons and electrons were well in place, and no major conceptual change was needed analogous to that which was necessitated by a finite and physically sensible account of the radiative behavior of hot objects, as provided by the Planck radiation law.

This "divergence problem" was solved in the case of quantum electrodynamics during the late 1940s and early 1950s by Hans Bethe, Tomonaga, Schwinger, Feynman, and Dyson, through the procedure known as renormalization. Great progress was made after realizing that ALL infinities in quantum electrodynamics are related to two effects: the self-energy of the electron/positron and vacuum polarization. Renormalization concerns the business of paying very careful attention to just what is meant by, for example, the very concepts "charge" and "mass" as they occur in the pure, non-interacting field-equations. The "vacuum" is itself polarizable and, hence, populated by virtual particle (on shell and off shell) pairs, and, hence, is a seething and busy dynamical system in its own right. This was a critical step in identifying the source of "infinities" and "divergences". The "bare mass" and the "bare charge" of a particle, the values that appear in the free-field equations (non-interacting case), are abstractions that are simply not realized in experiment (in interaction). What we measure, and hence, what we must take account of with our equations, and

what the solutions must account for, are the "renormalized mass" and the "renormalized charge" of a particle. That is to say, the "shifted" or "dressed" values these quantities must have when due care is taken to include all deviations from their "bare values" is dictated by the very nature of quantum fields themselves.

The first approach that bore fruit is known as the "interaction representation," (see the article Interaction picture) a Lorentz covariant and gauge-invariant generalization of time-dependent perturbation theory used in ordinary quantum mechanics, and developed by Tomonaga and Schwinger, generalizing earlier efforts of Dirac, Fock and Podolsky. Tomonaga and Schwinger invented a relativistically covariant scheme for representing field commutators and field operators intermediate between the two main representations of a quantum system, the Schrödinger and the Heisenberg representations (see the article on quantum mechanics). Within this scheme, field commutators at separated points can be evaluated in terms of "bare" field creation and annihilation operators. This allows for keeping track of the time-evolution of both the "bare" and "renormalized", or perturbed, values of the Hamiltonian and expresses everything in terms of the coupled, gauge invariant "bare" field-equations. Schwinger gave the most elegant formulation of this approach. The next and most famous development is due to Feynman, who, with his brilliant rules for assigning a "graph"/"diagram" to the terms in the scattering matrix (See S-Matrix Feynman diagrams). These directly corresponded (through the Schwinger-Dyson equation) to the measurable physical processes (cross sections, probability amplitudes, decay widths and lifetimes of excited states) one needs to be able to calculate. This revolutionized how quantum field theory calculations are carried-out in practice.

Two classic text-books from the 1960s, J.D. Bjorken and S.D. Drell, *Relativistic Quantum Mechanics* (1964) and J.J. Sakurai, *Advanced Quantum Mechanics* (1967), thoroughly developed the Feynman graph expansion techniques using physically intuitive and practical methods following from the correspondence principle, without worrying about the technicalities involved in deriving the Feynman rules from the superstructure of quantum field theory itself. Although both Feynman's heuristic and pictorial style of dealing with the infinities, as well as the formal methods of Tomonaga and Schwinger, worked extremely well, and gave spectacularly accurate answers, the true analytical nature of the question of "renormalizability", that is, whether ANY theory formulated as a "quantum field theory" would give finite answers, was not worked-out till much later, when the urgency of trying to formulate finite theories for the strong and electro-weak (and gravitational interactions) demanded its solution.

Renormalization in the case of QED was largely fortuitous due to the smallness of the coupling constant, the fact that the coupling has no dimensions involving mass, the so-called fine structure constant, and also the zero-mass of the gauge boson involved, the photon, rendered the small-distance/high-energy behavior of QED manageable. Also, electromagnetic processes are very "clean" in the sense that they are not badly suppressed/damped and/or hidden by the other gauge interactions. By 1958 Sidney Drell observed: "Quantum electrodynamics (QED) has achieved a status of peaceful coexistence with its divergences...."

The unification of the electromagnetic force with the weak force encountered initial difficulties due to the lack of accelerator energies high enough to reveal processes beyond the Fermi interaction range. Additionally, a satisfactory theoretical understanding of hadron substructure had to be developed, culminating in the quark model.

In the case of the strong interactions, progress concerning their short-distance/high-energy behavior was much slower and more frustrating. For strong interactions with the electro-weak fields, there were difficult issues regarding the strength of coupling, the mass generation of the force carriers as well as their non-linear, self interactions. Although there has been theoretical progress toward a grand unified quantum field theory incorporating the electro-magnetic force, the weak force and the strong force, empirical verification is still pending. Superunification, incorporating the gravitational force, is still very speculative, and is under intensive investigation by many of the best minds in contemporary theoretical physics. Gravitation is a tensor field description of a spin-2 gauge-boson, the "graviton", and is further discussed in the articles on general relativity and quantum gravity.

From the point of view of the techniques of (four-dimensional) quantum field theory, and as the numerous and heroic efforts to formulate a consistent quantum gravity theory by some very able minds attests, gravitational quantization was, and is still, the reigning champion for bad behavior. There are problems and frustrations stemming from the fact

that the gravitational coupling constant has dimensions involving inverse powers of mass, and as a simple consequence, it is plagued by badly behaved (in the sense of perturbation theory) non-linear and violent self-interactions. Gravity, basically, gravitates, which in turn...gravitates...and so on, (i.e., gravity is itself a source of gravity,...) thus creating a nightmare at all orders of perturbation theory. Also, gravity couples to all energy equally strongly, as per the equivalence principle, so this makes the notion of ever really "switching-off", "cutting-off" or separating, the gravitational interaction from other interactions ambiguous and impossible since, with gravitation, we are dealing with the very structure of space-time itself. (See general covariance and, for a modest, yet highly non-trivial and significant interplay between (QFT) and gravitation (spacetime), see the article Hawking radiation and references cited therein. Also quantum field theory in curved spacetime).

Thanks to the somewhat brute-force, clanky and heuristic methods of Feynman, and the elegant and abstract methods of Tomonaga/Schwinger, from the period of early renormalization, we do have the modern theory of quantum electrodynamics (QED). It is still the most accurate physical theory known, the prototype of a successful quantum field theory. Beginning in the 1950s with the work of Yang and Mills, as well as Ryoyu Utiyama, following the previous lead of Weyl and Pauli, deep explorations illuminated the types of symmetries and invariances any field theory must satisfy. QED, and indeed, all field theories, were generalized to a class of quantum field theories known as gauge theories. Quantum electrodynamics is the most famous example of what is known as an Abelian gauge theory. It relies on the symmetry group $U(1)$ and has one massless gauge field, the $U(1)$ gauge symmetry, dictating the form of the interactions involving the electromagnetic field, with the photon being the gauge boson. That symmetries dictate, limit and necessitate the form of interaction between particles is the essence of the "gauge theory revolution." Yang and Mills formulated the first explicit example of a non-Abelian gauge theory, Yang-Mills theory, with an attempted explanation of the strong interactions in mind. The strong interactions were then (incorrectly) understood in the mid-1950s, to be mediated by the pi-mesons, the particles predicted by Hideki Yukawa in 1935, based on his profound reflections concerning the reciprocal connection between the mass of any force-mediating particle and the range of the force it mediates. This was allowed by the uncertainty principle. The 1960s and 1970s saw the formulation of a gauge theory now known as the Standard Model of particle physics, which systematically describes the elementary particles and the interactions between them.

The electroweak interaction part of the standard model was formulated by Sheldon Glashow in the years 1958-60 with his discovery of the $SU(2) \times U(1)$ group structure of the theory. Steven Weinberg and Abdus Salam brilliantly invoked the Anderson-Higgs mechanism for the generation of the W's and Z masses (the intermediate vector boson(s) responsible for the weak interactions and neutral-currents) and keeping the mass of the photon zero. The Goldstone/Higgs idea for generating mass in gauge theories was sparked in the late 1950s and early 1960s when a number of theoreticians (including Yoichiro Nambu, Steven Weinberg, Jeffrey Goldstone, François Englert, Robert Brout, G. S. Guralnik, C. R. Hagen, Tom Kibble and Philip Warren Anderson) noticed a possibly useful analogy to the (spontaneous) breaking of the $U(1)$ symmetry of electromagnetism in the formation of the BCS ground-state of a superconductor. The gauge boson involved in this situation, the photon, behaves as though it has acquired a finite mass. There is a further possibility that the physical vacuum (ground-state) does not respect the symmetries implied by the "unbroken" electroweak Lagrangian (see the article Electroweak interaction for more details) from which one arrives at the field equations. The electroweak theory of Weinberg and Salam was shown to be renormalizable (finite) and hence consistent by Gerardus 't Hooft and Martinus Veltman. The Glashow-Weinberg-Salam theory (GWS-Theory) is a triumph and, in certain applications, gives an accuracy on a par with quantum electrodynamics.

Also during the 1970s parallel developments in the study of phase transitions in condensed matter physics led Leo Kadanoff, Michael Fisher and Kenneth Wilson (extending work of Ernst Stueckelberg, Andre Peterman, Murray Gell-Mann, and Francis Low) to a set of ideas and methods known as the renormalization group. By providing a better physical understanding of the renormalization procedure invented in the 1940s, the renormalization group sparked what has been called the "grand synthesis" of theoretical physics, uniting the quantum field theoretical techniques used in particle physics and condensed matter physics into a single theoretical framework.

The study of quantum field theory is alive and flourishing, as are applications of this method to many physical problems. It remains one of the most vital areas of theoretical physics today, providing a common language to many branches of physics.

Principles of quantum field theory

Classical fields and quantum fields

Quantum mechanics, in its most general formulation, is a theory of abstract operators (observables) acting on an abstract state space (Hilbert space), where the observables represent physically observable quantities and the state space represents the possible states of the system under study. Furthermore, each observable corresponds, in a technical sense, to the classical idea of a degree of freedom. For instance, the fundamental observables associated with the motion of a single quantum mechanical particle are the position and momentum operators $\hat{x}$ and $\hat{p}$.

Ordinary quantum mechanics deals with systems such as this, which possess a small set of degrees of freedom.

(It is important to note, at this point, that this article does not use the word "particle" in the context of wave–particle duality. In quantum field theory, "particle" is a generic term for any discrete quantum mechanical entity, such as an electron or photon, which can behave like classical particles or classical waves under different experimental conditions.)

A **quantum field** is a quantum mechanical system containing a large, and possibly infinite, number of degrees of freedom. A classical field contains a set of degrees of freedom at each point of space; for instance, the classical electromagnetic field defines two vectors — the electric field and the magnetic field — that can in principle take on distinct values for each position $\mathbf{r}$. When the field *as a whole* is considered as a quantum mechanical system, its observables form an infinite (in fact uncountable) set, because $\mathbf{r}$ is continuous.

Furthermore, the degrees of freedom in a quantum field are arranged in "repeated" sets. For example, the degrees of freedom in an electromagnetic field can be grouped according to the position $\mathbf{r}$, with exactly two vectors for each $\mathbf{r}$. Note that $\mathbf{r}$ is an ordinary number that "indexes" the observables; it is not to be confused with the position operator $\hat{x}$ encountered in ordinary quantum mechanics, which is an observable. (Thus, ordinary quantum mechanics is sometimes referred to as "zero-dimensional quantum field theory", because it contains only a single set of observables.)

It is also important to note that there is nothing special about $\mathbf{r}$ because, as it turns out, there is generally more than one way of indexing the degrees of freedom in the field.

In the following sections, we will show how these ideas can be used to construct a quantum mechanical theory with the desired properties. We will begin by discussing single-particle quantum mechanics and the associated theory of many-particle quantum mechanics. Then, by finding a way to index the degrees of freedom in the many-particle problem, we will construct a quantum field and study its implications.

Single-particle and many-particle quantum mechanics

In quantum mechanics, the time-dependent Schrödinger equation for a single particle is

$$-\frac{\hbar^2}{2m} \frac{\partial^2}{\partial x^2} \psi(x, t) + V(x) \psi(x, t) = i\hbar \frac{\partial}{\partial t} \psi(x, t),$$

where m is the particle's mass, V is the applied potential, and $\psi(x, t)$ denotes the wavefunction.

We wish to consider how this problem generalizes to N particles. There are two motivations for studying the many-particle problem. The first is a straightforward need in condensed matter physics, where typically the number of particles is on the order of Avogadro's number (6.0221415×10^{23}). The second motivation for the many-particle problem arises from particle physics and the desire to incorporate the effects of special relativity. If one attempts to include the relativistic rest energy into the above equation (in quantum mechanics where position is an observable),

the result is either the Klein-Gordon equation or the Dirac equation. However, these equations have many unsatisfactory qualities; for instance, they possess energy eigenvalues that extend to $-\infty$, so that there seems to be no easy definition of a ground state. It turns out that such inconsistencies arise from relativistic wavefunctions having a probabilistic interpretation in position space, as probability conservation is not a relativistically covariant concept. In quantum field theory, unlike in quantum mechanics, position is not an observable, and thus, one does not need the concept of a position-space probability density. For quantum fields whose interaction can be treated perturbatively, this is equivalent to neglecting the possibility of dynamically creating or destroying particles, which is a crucial aspect of relativistic quantum theory. Einstein's famous mass-energy relation allows for the possibility that sufficiently massive particles can decay into several lighter particles, and sufficiently energetic particles can combine to form massive particles. For example, an electron and a positron can annihilate each other to create photons. This suggests that a consistent relativistic quantum theory should be able to describe many-particle dynamics.

Furthermore, we will assume that the N particles are indistinguishable. As described in the article on identical particles, this implies that the state of the entire system must be either symmetric (bosons) or antisymmetric (fermions) when the coordinates of its constituent particles are exchanged. These multi-particle states are rather complicated to write. For example, the general quantum state of a system of N bosons is written as

$$|\phi_1 \cdots \phi_N\rangle = \sqrt{\frac{\prod_j N_j!}{N!}} \sum_{p \in S_N} |\phi_{p(1)}\rangle \cdots |\phi_{p(N)}\rangle,$$

where $|\phi_i\rangle$ are the single-particle states, N_j is the number of particles occupying state j , and the sum is taken over all possible permutations p acting on N elements. In general, this is a sum of $N!$ (N factorial) distinct terms, which quickly becomes unmanageable as N increases. The way to simplify this problem is to turn it into a quantum field theory.

Second quantization

In this section, we will describe a method for constructing a quantum field theory called **second quantization**. This basically involves choosing a way to index the quantum mechanical degrees of freedom in the space of multiple identical-particle states. It is based on the Hamiltonian formulation of quantum mechanics; several other approaches exist, such as the Feynman path integral,^[4] which uses a Lagrangian formulation. For an overview, see the article on quantization.

Second quantization of bosons

For simplicity, we will first discuss second quantization for bosons, which form perfectly symmetric quantum states. Let us denote the mutually orthogonal single-particle states by $|\phi_1\rangle, |\phi_2\rangle, |\phi_3\rangle$, and so on. For example, the 3-particle state with one particle in state $|\phi_1\rangle$ and two in state $|\phi_2\rangle$ is

$$\frac{1}{\sqrt{3}} [|\phi_1\rangle|\phi_2\rangle|\phi_2\rangle + |\phi_2\rangle|\phi_1\rangle|\phi_2\rangle + |\phi_2\rangle|\phi_2\rangle|\phi_1\rangle].$$

The first step in second quantization is to express such quantum states in terms of **occupation numbers**, by listing the number of particles occupying each of the single-particle states $|\phi_1\rangle, |\phi_2\rangle$, etc. This is simply another way of labelling the states. For instance, the above 3-particle state is denoted as

$$|1, 2, 0, 0, 0, \dots\rangle.$$

The next step is to expand the N -particle state space to include the state spaces for all possible values of N . This extended state space, known as a Fock space, is composed of the state space of a system with no particles (the so-called vacuum state), plus the state space of a 1-particle system, plus the state space of a 2-particle system, and so forth. It is easy to see that there is a one-to-one correspondence between the occupation number representation and valid boson states in the Fock space.

At this point, the quantum mechanical system has become a quantum field in the sense we described above. The field's elementary degrees of freedom are the occupation numbers, and each occupation number is indexed by a number $j \dots$, indicating which of the single-particle states $|\phi_1\rangle, |\phi_2\rangle, \dots |\phi_j\rangle \dots$ it refers to.

The properties of this quantum field can be explored by defining creation and annihilation operators, which add and subtract particles. They are analogous to "ladder operators" in the quantum harmonic oscillator problem, which added and subtracted energy quanta. However, these operators literally create and annihilate particles of a given quantum state. The bosonic annihilation operator a_2 and creation operator $a_2^\dagger$ have the following effects:

$$a_2 |N_1, N_2, N_3, \dots\rangle = \sqrt{N_2} |N_1, (N_2 - 1), N_3, \dots\rangle,$$

$$a_2^\dagger |N_1, N_2, N_3, \dots\rangle = \sqrt{N_2 + 1} |N_1, (N_2 + 1), N_3, \dots\rangle.$$

It can be shown that these are operators in the usual quantum mechanical sense, i.e. linear operators acting on the Fock space. Furthermore, they are indeed Hermitian conjugates, which justifies the way we have written them. They can be shown to obey the commutation relation

$$[a_i, a_j] = 0 \quad , \quad [a_i^\dagger, a_j^\dagger] = 0 \quad , \quad [a_i, a_j^\dagger] = \delta_{ij},$$

where δ stands for the Kronecker delta. These are precisely the relations obeyed by the ladder operators for an infinite set of independent quantum harmonic oscillators, one for each single-particle state. Adding or removing bosons from each state is therefore analogous to exciting or de-exciting a quantum of energy in a harmonic oscillator.

The Hamiltonian of the quantum field (which, through the Schrödinger equation, determines its dynamics) can be written in terms of creation and annihilation operators. For instance, the Hamiltonian of a field of free (non-interacting) bosons is

$$H = \sum_{\mathbf{k}} E_{\mathbf{k}} a_{\mathbf{k}}^\dagger a_{\mathbf{k}},$$

where $E_{\mathbf{k}}$ is the energy of the $\mathbf{k}$ -th single-particle energy eigenstate. Note that

$$a_{\mathbf{k}}^\dagger a_{\mathbf{k}} |\dots, N_{\mathbf{k}}, \dots\rangle = N_{\mathbf{k}} |\dots, N_{\mathbf{k}}, \dots\rangle.$$

Second quantization of fermions

It turns out that a different definition of creation and annihilation must be used for describing fermions. According to the Pauli exclusion principle, fermions cannot share quantum states, so their occupation numbers N_i can only take on the value 0 or 1. The fermionic annihilation operators c and creation operators $c^\dagger$ are defined by their actions on a Fock state thus

$$c_j |N_1, N_2, \dots, N_j = 0, \dots\rangle = 0$$

$$c_j |N_1, N_2, \dots, N_j = 1, \dots\rangle = (-1)^{(N_1 + \dots + N_{j-1})} |N_1, N_2, \dots, N_j = 0, \dots\rangle$$

$$c_j^\dagger |N_1, N_2, \dots, N_j = 0, \dots\rangle = (-1)^{(N_1 + \dots + N_{j-1})} |N_1, N_2, \dots, N_j = 1, \dots\rangle$$

$$c_j^\dagger |N_1, N_2, \dots, N_j = 1, \dots\rangle = 0.$$

These obey an anticommutation relation:

$$\{c_i, c_j\} = 0 \quad , \quad \{c_i^\dagger, c_j^\dagger\} = 0 \quad , \quad \{c_i, c_j^\dagger\} = \delta_{ij}.$$

One may notice from this that applying a fermionic creation operator twice gives zero, so it is impossible for the particles to share single-particle states, in accordance with the exclusion principle.

Field operators

We have previously mentioned that there can be more than one way of indexing the degrees of freedom in a quantum field. Second quantization indexes the field by enumerating the single-particle quantum states. However, as we have discussed, it is more natural to think about a "field", such as the electromagnetic field, as a set of degrees of freedom indexed by position.

To this end, we can define *field operators* that create or destroy a particle at a particular point in space. In particle physics, these operators turn out to be more convenient to work with, because they make it easier to formulate theories that satisfy the demands of relativity.

Single-particle states are usually enumerated in terms of their momenta (as in the particle in a box problem.) We can construct field operators by applying the Fourier transform to the creation and annihilation operators for these states. For example, the bosonic field annihilation operator $\phi(\mathbf{r})$ is

$$\phi(\mathbf{r}) \stackrel{\text{def}}{=} \sum_j e^{i\mathbf{k}_j \cdot \mathbf{r}} a_j.$$

The bosonic field operators obey the commutation relation

$$[\phi(\mathbf{r}), \phi(\mathbf{r}')] = 0 \quad , \quad [\phi^\dagger(\mathbf{r}), \phi^\dagger(\mathbf{r}')] = 0 \quad , \quad [\phi(\mathbf{r}), \phi^\dagger(\mathbf{r}')] = \delta^3(\mathbf{r} - \mathbf{r}')$$

where $\delta(x)$ stands for the Dirac delta function. As before, the fermionic relations are the same, with the commutators replaced by anticommutators.

It should be emphasized that the field operator is *not* the same thing as a single-particle wavefunction. The former is an operator acting on the Fock space, and the latter is a quantum-mechanical amplitude for finding a particle in some position. However, they are closely related, and are indeed commonly denoted with the same symbol. If we have a Hamiltonian with a space representation, say

$$H = -\frac{\hbar^2}{2m} \sum_i \nabla_i^2 + \sum_{i < j} U(|\mathbf{r}_i - \mathbf{r}_j|)$$

where the indices i and j run over all particles, then the field theory Hamiltonian (in the non-relativistic limit and for negligible self-interactions) is

$$H = -\frac{\hbar^2}{2m} \int d^3r \phi^\dagger(\mathbf{r}) \nabla^2 \phi(\mathbf{r}) + \int d^3r \int d^3r' \phi^\dagger(\mathbf{r}) \phi^\dagger(\mathbf{r}') U(|\mathbf{r} - \mathbf{r}'|) \phi(\mathbf{r}') \phi(\mathbf{r}).$$

This looks remarkably like an expression for the expectation value of the energy, with ϕ playing the role of the wavefunction. This relationship between the field operators and wavefunctions makes it very easy to formulate field theories starting from space-projected Hamiltonians.

Implications of quantum field theory

Unification of fields and particles

The "second quantization" procedure that we have outlined in the previous section takes a set of single-particle quantum states as a starting point. Sometimes, it is impossible to define such single-particle states, and one must proceed directly to quantum field theory. For example, a quantum theory of the electromagnetic field *must* be a quantum field theory, because it is impossible (for various reasons) to define a wavefunction for a single photon. In such situations, the quantum field theory can be constructed by examining the mechanical properties of the classical field and guessing the corresponding quantum theory. For free (non-interacting) quantum fields, the quantum field theories obtained in this way have the same properties as those obtained using second quantization, such as well-defined creation and annihilation operators obeying commutation or anticommutation relations.

Quantum field theory thus provides a unified framework for describing "field-like" objects (such as the electromagnetic field, whose excitations are photons) and "particle-like" objects (such as electrons, which are treated

as excitations of an underlying electron field), so long as one can treat interactions as "perturbations" of free fields. There are still unsolved problems relating to the more general case of interacting fields that may or may not be adequately described by perturbation theory. For more on this topic, see Haag's theorem.

Physical meaning of particle indistinguishability

The second quantization procedure relies crucially on the particles being identical. We would not have been able to construct a quantum field theory from a distinguishable many-particle system, because there would have been no way of separating and indexing the degrees of freedom.

Many physicists prefer to take the converse interpretation, which is that *quantum field theory explains what identical particles are*. In ordinary quantum mechanics, there is not much theoretical motivation for using symmetric (bosonic) or antisymmetric (fermionic) states, and the need for such states is simply regarded as an empirical fact. From the point of view of quantum field theory, particles are identical if and only if they are excitations of the same underlying quantum field. Thus, the question "why are all electrons identical?" arises from mistakenly regarding individual electrons as fundamental objects, when in fact it is only the electron field that is fundamental.

Particle conservation and non-conservation

During second quantization, we started with a Hamiltonian and state space describing a fixed number of particles (N), and ended with a Hamiltonian and state space for an arbitrary number of particles. Of course, in many common situations N is an important and perfectly well-defined quantity, e.g. if we are describing a gas of atoms sealed in a box. From the point of view of quantum field theory, such situations are described by quantum states that are eigenstates of the number operator $\hat{N}$, which measures the total number of particles present. As with any quantum mechanical observable, $\hat{N}$ is conserved if it commutes with the Hamiltonian. In that case, the quantum state is trapped in the N -particle subspace of the total Fock space, and the situation could equally well be described by ordinary N -particle quantum mechanics. (Strictly speaking, this is only true in the noninteracting case or in the low energy density limit of renormalized quantum field theories)

For example, we can see that the free-boson Hamiltonian described above conserves particle number. Whenever the Hamiltonian operates on a state, each particle destroyed by an annihilation operator a_k is immediately put back by the creation operator $a_k^\dagger$.

On the other hand, it is possible, and indeed common, to encounter quantum states that are *not* eigenstates of $\hat{N}$, which do not have well-defined particle numbers. Such states are difficult or impossible to handle using ordinary quantum mechanics, but they can be easily described in quantum field theory as quantum superpositions of states having different values of N . For example, suppose we have a bosonic field whose particles can be created or destroyed by interactions with a fermionic field. The Hamiltonian of the combined system would be given by the Hamiltonians of the free boson and free fermion fields, plus a "potential energy" term such as

$$H_I = \sum_{k,q} V_q (a_q + a_{-q}^\dagger) c_{k+q}^\dagger c_k,$$

where $a_k^\dagger$ and a_k denotes the bosonic creation and annihilation operators, $c_k^\dagger$ and c_k denotes the fermionic creation and annihilation operators, and V_q is a parameter that describes the strength of the interaction. This "interaction term" describes processes in which a fermion in state k either absorbs or emits a boson, thereby being kicked into a different eigenstate $k + q$. (In fact, this type of Hamiltonian is used to describe interaction between conduction electrons and phonons in metals. The interaction between electrons and photons is treated in a similar way, but is a little more complicated because the role of spin must be taken into account.) One thing to notice here is that even if we start out with a fixed number of bosons, we will typically end up with a superposition of states with different numbers of bosons at later times. The number of fermions, however, is conserved in this case. In condensed matter physics, states with ill-defined particle numbers are particularly important for describing the various superfluids. Many of the defining characteristics of a superfluid arise from the notion that its quantum state is

a superposition of states with different particle numbers. In addition, the concept of a coherent state (used to model the laser and the BCS ground state) refers to a state with an ill-defined particle number but a well-defined phase.

Axiomatic approaches

The preceding description of quantum field theory follows the spirit in which most physicists approach the subject. However, it is not mathematically rigorous. Over the past several decades, there have been many attempts to put quantum field theory on a firm mathematical footing by formulating a set of axioms for it. These attempts fall into two broad classes.

The first class of axioms, first proposed during the 1950s, include the Wightman, Osterwalder-Schrader, and Haag-Kastler systems. They attempted to formalize the physicists' notion of an "operator-valued field" within the context of functional analysis, and enjoyed limited success. It was possible to prove that any quantum field theory satisfying these axioms satisfied certain general theorems, such as the spin-statistics theorem and the CPT theorem. Unfortunately, it proved extraordinarily difficult to show that any realistic field theory, including the Standard Model, satisfied these axioms. Most of the theories that could be treated with these analytic axioms were physically trivial, being restricted to low-dimensions and lacking interesting dynamics. The construction of theories satisfying one of these sets of axioms falls in the field of constructive quantum field theory. Important work was done in this area in the 1970s by Segal, Glimm, Jaffe and others.

During the 1980s, a second set of axioms based on geometric ideas was proposed. This line of investigation, which restricts its attention to a particular class of quantum field theories known as topological quantum field theories, is associated most closely with Michael Atiyah and Graeme Segal, and was notably expanded upon by Edward Witten, Richard Borcherds, and Maxim Kontsevich. However, most of the physically relevant quantum field theories, such as the Standard Model, are not topological quantum field theories; the quantum field theory of the fractional quantum Hall effect is a notable exception. The main impact of axiomatic topological quantum field theory has been on mathematics, with important applications in representation theory, algebraic topology, and differential geometry.

Finding the proper axioms for quantum field theory is still an open and difficult problem in mathematics. One of the Millennium Prize Problems—proving the existence of a mass gap in Yang-Mills theory—is linked to this issue.

Phenomena associated with quantum field theory

In the previous part of the article, we described the most general properties of quantum field theories. Some of the quantum field theories studied in various fields of theoretical physics possess additional special properties, such as renormalizability, gauge symmetry, and supersymmetry. These are described in the following sections.

Renormalization

Early in the history of quantum field theory, it was found that many seemingly innocuous calculations, such as the perturbative shift in the energy of an electron due to the presence of the electromagnetic field, give infinite results. The reason is that the perturbation theory for the shift in an energy involves a sum over all other energy levels, and there are infinitely many levels at short distances that each give a finite contribution.

Many of these problems are related to failures in classical electrodynamics that were identified but unsolved in the 19th century, and they basically stem from the fact that many of the supposedly "intrinsic" properties of an electron are tied to the electromagnetic field that it carries around with it. The energy carried by a single electron— its self energy— is not simply the bare value, but also includes the energy contained in its electromagnetic field, its attendant cloud of photons. The energy in a field of a spherical source diverges in both classical and quantum mechanics, but as discovered by Weisskopf, in quantum mechanics the divergence is much milder, going only as the logarithm of the radius of the sphere.

The solution to the problem, presciently suggested by Stueckelberg, independently by Bethe after the crucial experiment by Lamb, implemented at one loop by Schwinger, and systematically extended to all loops by Feynman and Dyson, with converging work by Tomonaga in isolated postwar Japan, is called renormalization. The technique of renormalization recognizes that the problem is essentially purely mathematical, that extremely short distances are at fault. In order to define a theory on a continuum, first place a cutoff on the fields, by postulating that quanta cannot have energies above some extremely high value. This has the effect of replacing continuous space by a structure where very short wavelengths do not exist, as on a lattice. Lattices break rotational symmetry, and one of the crucial contributions made by Feynman, Pauli and Villars, and modernized by 't Hooft and Veltman, is a symmetry preserving cutoff for perturbation theory. There is no known symmetrical cutoff outside of perturbation theory, so for rigorous or numerical work people often use an actual lattice.

On a lattice, every quantity is finite but depends on the spacing. When taking the limit of zero spacing, we make sure that the physically observable quantities like the observed electron mass stay fixed, which means that the constants in the Lagrangian defining the theory depend on the spacing. Hopefully, by allowing the constants to vary with the lattice spacing, all the results at long distances become insensitive to the lattice, defining a continuum limit.

The renormalization procedure only works for a certain class of quantum field theories, called **renormalizable quantum field theories**. A theory is **perturbatively renormalizable** when the constants in the Lagrangian only diverge at worst as logarithms of the lattice spacing for very short spacings. The continuum limit is then well defined in perturbation theory, and even if it is not fully well defined non-perturbatively, the problems only show up at distance scales that are exponentially small in the inverse coupling for weak couplings. The Standard Model of particle physics is perturbatively renormalizable, and so are its component theories (quantum electrodynamics/electroweak theory and quantum chromodynamics). Of the three components, quantum electrodynamics is believed to not have a continuum limit, while the asymptotically free SU(2) and SU(3) weak hypercharge and strong color interactions are nonperturbatively well defined.

The renormalization group describes how renormalizable theories emerge as the long distance low-energy effective field theory for any given high-energy theory. Because of this, renormalizable theories are insensitive to the precise nature of the underlying high-energy short-distance phenomena. This is a blessing because it allows physicists to formulate low energy theories without knowing the details of high energy phenomenon. It is also a curse, because once a renormalizable theory like the standard model is found to work, it gives very few clues to higher energy processes. The only way high energy processes can be seen in the standard model is when they allow otherwise forbidden events, or if they predict quantitative relations between the coupling constants.

Gauge freedom

A gauge theory is a theory that admits a symmetry with a local parameter. For example, in every quantum theory the global phase of the wave function is arbitrary and does not represent something physical. Consequently, the theory is invariant under a global change of phases (adding a constant to the phase of all wave functions, everywhere); this is a global symmetry. In quantum electrodynamics, the theory is also invariant under a *local* change of phase, that is - one may shift the phase of all wave functions so that the shift may be different at every point in space-time. This is a *local* symmetry. However, in order for a well-defined derivative operator to exist, one must introduce a new field, the gauge field, which also transforms in order for the local change of variables (the phase in our example) not to affect the derivative. In quantum electrodynamics this gauge field is the electromagnetic field. The change of local gauge of variables is termed gauge transformation.

In quantum field theory the excitations of fields represent particles. The particle associated with excitations of the gauge field is the gauge boson, which is the photon in the case of quantum electrodynamics.

The degrees of freedom in quantum field theory are local fluctuations of the fields. The existence of a gauge symmetry reduces the number of degrees of freedom, simply because some fluctuations of the fields can be transformed to zero by gauge transformations, so they are equivalent to having no fluctuations at all, and they

therefore have no physical meaning. Such fluctuations are usually called "non-physical degrees of freedom" or *gauge artifacts*; usually some of them have a negative norm, making them inadequate for a consistent theory. Therefore, if a classical field theory has a gauge symmetry, then its quantized version (i.e. the corresponding quantum field theory) will have this symmetry as well. In other words, a gauge symmetry cannot have a quantum anomaly. If a gauge symmetry is anomalous (i.e. not kept in the quantum theory) then the theory is non-consistent: for example, in quantum electrodynamics, had there been a gauge anomaly, this would require the appearance of photons with longitudinal polarization and polarization in the time direction, the latter having a negative norm, rendering the theory inconsistent; another possibility would be for these photons to appear only in intermediate processes but not in the final products of any interaction, making the theory non unitary and again inconsistent (see optical theorem).

In general, the gauge transformations of a theory consist of several different transformations, which may not be commutative. These transformations are together described by a mathematical object known as a gauge group. Infinitesimal gauge transformations are the gauge group generators. Therefore the number of gauge bosons is the group dimension (i.e. number of generators forming a basis).

All the fundamental interactions in nature are described by gauge theories. These are:

- Quantum electrodynamics, whose gauge transformation is a local change of phase, so that the gauge group is $U(1)$. The gauge boson is the photon.
- Quantum chromodynamics, whose gauge group is $SU(3)$. The gauge bosons are eight gluons.
- The electroweak Theory, whose gauge group is $U(1) \otimes SU(2)$ (a direct product of $U(1)$ and $SU(2)$).
- Gravity, whose classical theory is general relativity, admits the equivalence principle, which is a form of gauge symmetry. However, it is explicitly non-renormalizable.

Multivalued Gauge Transformations

The gauge transformations which leave the theory invariant involve by definition only single-valued gauge functions $\Lambda(x_i)$ which satisfy the Schwarz integrability criterion

$$\partial_{x_i x_j} \Lambda = \partial_{x_j x_i} \Lambda.$$

An interesting extension of gauge transformations arises if the gauge functions $\Lambda(x_i)$ are allowed to be multivalued functions which violate the integrability criterion. These are capable of changing the physical field strengths and are therefore no proper symmetry transformations. Nevertheless, the transformed field equations describe correctly the physical laws in the presence of the newly generated field strengths. See the textbook by H. Kleinert cited below for the applications to phenomena in physics.

Supersymmetry

Supersymmetry assumes that every fundamental fermion has a superpartner that is a boson and vice versa. It was introduced in order to solve the so-called Hierarchy Problem, that is, to explain why particles not protected by any symmetry (like the Higgs boson) do not receive radiative corrections to its mass driving it to the larger scales (GUT, Planck...). It was soon realized that supersymmetry has other interesting properties: its gauged version is an extension of general relativity (Supergravity), and it is a key ingredient for the consistency of string theory.

The way supersymmetry protects the hierarchies is the following: since for every particle there is a superpartner with the same mass, any loop in a radiative correction is cancelled by the loop corresponding to its superpartner, rendering the theory UV finite.

Since no superpartners have yet been observed, if supersymmetry exists it must be broken (through a so-called soft term, which breaks supersymmetry without ruining its helpful features). The simplest models of this breaking require that the energy of the superpartners not be too high; in these cases, supersymmetry is expected to be observed by experiments at the Large Hadron Collider.

See also

- List of quantum field theories
- Constructive quantum field theory
- Feynman path integral
- Quantum chromodynamics
- Quantum electrodynamics
- Quantum flavordynamics
- Quantum geometrodynamics
- Quantum hydrodynamics
- Quantum magnetodynamics
- Quantum triviality
- Schwinger-Dyson equation
- Einstein-Maxwell-Dirac equations
- Relation between Schrödinger's equation and the path integral formulation of quantum mechanics
- Basic concepts of quantum mechanics
- Relationship between string theory and quantum field theory
- Abraham-Lorentz force
- Form factor
- Photon polarization
- Theoretical and experimental justification for the Schrödinger equation
- Invariance mechanics
- Green–Kubo relations
- Green's function (many-body theory)
- Common integrals in quantum field theory
- Wheeler-Feynman absorber theory
- Wigner's theorem
- Wigner's classification
- Static forces and virtual-particle exchange

Notes

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Further reading

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External links

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- Quantum Field Theory Video Lectures (<http://www.physics.harvard.edu/about/Phys253.html>) by Sidney R. Coleman
- Quantum Field Theory Lecture Notes (http://www.physics.gla.ac.uk/~dmiller/lectures/RQF_1-6_2010.pdf) by D.J. Miller
- Quantum Field Theory Lecture Notes II (http://www.physics.gla.ac.uk/~dmiller/lectures/RQF_7-9_2010.pdf) by D.J. Miller

Nuclear physics

Nuclear physics is the field of physics that studies the building blocks and interactions of atomic nuclei. The most commonly known applications of nuclear physics are nuclear power generation and nuclear weapons technology, but the research has provided application in many fields, including those in nuclear medicine and magnetic resonance imaging, ion implantation in materials engineering, and radiocarbon dating in geology and archaeology.

The field of particle physics evolved out of nuclear physics and is typically taught in close association with nuclear physics.

History

The history of nuclear physics as a discipline distinct from atomic physics starts with the discovery of radioactivity by Henri Becquerel in 1896,^[1] while investigating phosphorescence in uranium salts.^[2] The discovery of the electron by J. J. Thomson a year later was an indication that the atom had internal structure. At the turn of the 20th century the accepted model of the atom was J. J. Thomson's *plum pudding* model in which the atom was a large positively charged ball with small negatively charged electrons embedded inside of it. By the turn of the century physicists had also discovered three types of radiation emanating from atoms, which they named alpha, beta, and gamma radiation. Experiments in 1911 by Lise Meitner and Otto Hahn, and by James Chadwick in 1914 discovered that the beta decay spectrum was continuous rather than discrete. That is, electrons were ejected from the atom with a range of energies, rather than the discrete amounts of energies that were observed in gamma and alpha decays. This was a problem for nuclear physics at the time, because it indicated that energy was not conserved in these decays.

In 1905, Albert Einstein formulated the idea of mass–energy equivalence. While the work on radioactivity by Becquerel, Pierre and Marie Curie predates this, an explanation of the source of the energy of radioactivity would have to wait for the discovery that the nucleus itself was composed of smaller constituents, the nucleons.

Rutherford's team discovers the nucleus

In 1907 Ernest Rutherford published "Radiation of the α Particle from Radium in passing through Matter."^[3] Geiger expanded on this work in a communication to the Royal Society^[4] with experiments he and Rutherford had done passing α particles through air, aluminum foil and gold leaf. More work was published in 1909 by Geiger and Marsden^[5] and further greatly expanded work was published in 1910 by Geiger,^[6] In 1911-2 Rutherford went before the Royal Society to explain the experiments and propound the new theory of the atomic nucleus as we now understand it.

The key experiment behind this announcement happened in 1910 at the University of Manchester, as Ernest Rutherford's team performed a remarkable experiment in which Hans Geiger and Ernest Marsden under his supervision fired alpha particles (helium nuclei) at a thin film of gold foil. The plum pudding model predicted that the alpha particles should come out of the foil with their trajectories being at most slightly bent. Rutherford had the idea to instruct his team to look for something that shocked him to actually observe: a few particles were scattered through large angles, even completely backwards, in some cases. He likened it to firing a bullet at tissue paper and having it bounce off. The discovery, beginning with Rutherford's analysis of the data in 1911, eventually led to the Rutherford model of the atom, in which the atom has a very small, very dense nucleus containing most of its mass, and consisting of heavy positively charged particles with embedded electrons in order to balance out the charge (since the neutron was unknown). As an example, in this model (which is not the modern one) nitrogen-14 consisted of a nucleus with 14 protons and 7 electrons (21 total particles), and the nucleus was surrounded by 7 more orbiting electrons.

The Rutherford model worked quite well until studies of nuclear spin were carried out by Franco Rasetti at the California Institute of Technology in 1929. By 1925 it was known that protons and electrons had a spin of $1/2$, and in

the Rutherford model of nitrogen-14, 20 of the total 21 nuclear particles should have paired up to cancel each other's spin, and the final odd particle should have left the nucleus with a net spin of $1/2$. Rasetti discovered, however, that nitrogen-14 has a spin of 1.

James Chadwick discovers the neutron

In 1932 Chadwick realized that radiation that had been observed by Walther Bothe, Herbert L. Becker, Irène and Frédéric Joliot-Curie was actually due to a neutral particle of about the same mass as the proton, that he called the neutron (following a suggestion about the need for such a particle, by Rutherford). In the same year Dmitri Ivanenko suggested that neutrons were in fact spin $1/2$ particles and that the nucleus contained neutrons to explain the mass not due to protons, and that there were no electrons in the nucleus—only protons and neutrons. The neutron spin immediately solved the problem of the spin of nitrogen-14, as the one unpaired proton and one unpaired neutron in this model, each contribute a spin of $1/2$ in the same direction, for a final total spin of 1.

With the discovery of the neutron, scientists at last could calculate what fraction of binding energy each nucleus had, from comparing the nuclear mass with that of the protons and neutrons which composed it. Differences between nuclear masses were calculated in this way and—when nuclear reactions were measured—were found to agree with Einstein's calculation of the equivalence of mass and energy to high accuracy (within 1 percent as of in 1934).

Yukawa's meson postulated to bind nuclei

In 1935 Hideki Yukawa proposed the first significant theory of the strong force to explain how the nucleus holds together. In the Yukawa interaction a virtual particle, later called a meson, mediated a force between all nucleons, including protons and neutrons. This force explained why nuclei did not disintegrate under the influence of proton repulsion, and it also gave an explanation of why the attractive strong force had a more limited range than the electromagnetic repulsion between protons. Later, the discovery of the pi meson showed it to have the properties of Yukawa's particle.

With Yukawa's papers, the modern model of the atom was complete. The center of the atom contains a tight ball of neutrons and protons, which is held together by the strong nuclear force, unless it is too large. Unstable nuclei may undergo alpha decay, in which they emit an energetic helium nucleus, or beta decay, in which they eject an electron (or positron). After one of these decays the resultant nucleus may be left in an excited state, and in this case it decays to its ground state by emitting high energy photons (gamma decay).

The study of the strong and weak nuclear forces (the latter explained by Enrico Fermi via Fermi's interaction in 1934) led physicists to collide nuclei and electrons at ever higher energies. This research became the science of particle physics, the crown jewel of which is the standard model of particle physics which unifies the strong, weak, and electromagnetic forces.

Proca's equations of the massive vector boson field

Alexandru Proca was the first to develop and report the massive vector boson field equations and a theory of the mesonic field of nuclear forces before Yukawa's theory was published. Proca's equations were known to Wolfgang Pauli^[7] who mentioned the equations in his Nobel address, and they were also known to Yukawa, Wentzel, Taketani, Sakata, Kemmer, Heitler and Fröhlich who appreciated the content of Proca's equations for developing a theory of the atomic nuclei in Nuclear Physics.^{[8] [9] [10] [11] [12]}

Modern nuclear physics

A heavy nucleus can contain hundreds of nucleons which means that with some approximation it can be treated as a classical system, rather than a quantum-mechanical one. In the resulting liquid-drop model, the nucleus has an energy which arises partly from surface tension and partly from electrical repulsion of the protons. The liquid-drop model is able to reproduce many features of nuclei, including the general trend of binding energy with respect to mass number, as well as the phenomenon of nuclear fission.

Superimposed on this classical picture, however, are quantum-mechanical effects, which can be described using the nuclear shell model, developed in large part by Maria Goeppert-Mayer. Nuclei with certain numbers of neutrons and protons (the magic numbers 2, 8, 20, 50, 82, 126, ...) are particularly stable, because their shells are filled.

Other more complicated models for the nucleus have also been proposed, such as the interacting boson model, in which pairs of neutrons and protons interact as bosons, analogously to Cooper pairs of electrons.

Much of current research in nuclear physics relates to the study of nuclei under extreme conditions such as high spin and excitation energy. Nuclei may also have extreme shapes (similar to that of Rugby balls) or extreme neutron-to-proton ratios. Experimenters can create such nuclei using artificially induced fusion or nucleon transfer reactions, employing ion beams from an accelerator. Beams with even higher energies can be used to create nuclei at very high temperatures, and there are signs that these experiments have produced a phase transition from normal nuclear matter to a new state, the quark-gluon plasma, in which the quarks mingle with one another, rather than being segregated in triplets as they are in neutrons and protons.

Nuclear decay

Eighty elements have at least one stable isotope never observed to decay, amounting to a total of about 255 stable isotopes. However, thousands of isotopes have been characterized that are unstable. These radioisotopes decay over time scales ranging from fractions of a second to weeks, years, or billions of years.

The stability of a nucleus is highest when it falls into a certain range or balance of composition of neutrons and protons; too few or too many neutrons may cause it to decay. For example, in beta decay a nitrogen-16 atom (7 protons, 9 neutrons) is converted to an oxygen-16 atom (8 protons, 8 neutrons) within a few seconds of being created. In this decay a neutron in the nitrogen nucleus is converted into a proton and an electron and an antineutrino by the weak nuclear force. The element is transmuted to another element in by acquiring the created proton.

In alpha decay the radioactive element decays by emitting a helium nucleus (2 protons and 2 neutrons), giving another element, plus helium-4. In many cases this process continues through several steps of this kind, including other types of decays, until a stable element is formed.

In gamma decay, a nucleus decays from an excited state into a lower state by emitting a gamma ray. It is then stable. The element is not changed in the process.

Other more exotic decays are possible (see the main article). For example, in internal conversion decay, the energy from an excited nucleus may be used to eject one of the inner orbital electrons from the atom, in a process which produces high speed electrons, but is not beta decay, and (unlike beta decay) does not transmute one element to another.

Nuclear fusion

In nuclear fusion, two low mass nuclei come into very close contact with each other, so that the strong force fuses them. It requires a large amount of energy to overcome the repulsion between the nuclei for the strong or nuclear forces to produce this effect, therefore nuclear fusion can only take place at very high temperatures or high pressures. Once the process succeeds, a very large amount of energy is released and the combined nucleus assumes a lower energy level. The binding energy per nucleon increases with mass number up until nickel-62. Stars like the Sun are powered by the fusion of four protons into a helium nucleus, two positrons, and two neutrinos. The uncontrolled

fusion of hydrogen into helium is known as thermonuclear runaway. A frontier in current research at various institutions, for example the Joint European Torus (JET) and ITER, is the development of an economically viable method of using energy from a *controlled* fusion reaction.

Nuclear fission

Nuclear fission is the reverse process of fusion. For nuclei heavier than nickel-62 the binding energy per nucleon decreases with the mass number. It is therefore possible for energy to be released if a heavy nucleus breaks apart into two lighter ones.

The process of alpha decay is in essence a special type of spontaneous nuclear fission. This process produces a highly asymmetrical fission because the four particles which make up the alpha particle are especially tightly bound to each other, making production of this nucleus in fission particularly likely.

For certain of the heaviest nuclei which produce neutrons on fission, and which also easily absorb neutrons to initiate fission, a self-igniting type of neutron-initiated fission can be obtained, in a so-called chain reaction. Chain reactions were known in chemistry before physics, and in fact many familiar processes like fires and chemical explosions are chemical chain reactions. The fission or "nuclear" chain-reaction, using fission-produced neutrons, is the source of energy for nuclear power plants and fission type nuclear bombs, such as those detonated by the United States in Hiroshima and Nagasaki, Japan, at the end of World War II. Heavy nuclei such as uranium and thorium may undergo spontaneous fission, but they are much more likely to undergo decay by alpha decay.

For a neutron-initiated chain-reaction to occur, there must be a critical mass of the element present in a certain space under certain conditions (these conditions slow and conserve neutrons for the reactions). There is one known example of a natural nuclear fission reactor, which was active in two regions of Oklo, Gabon, Africa, over 1.5 billion years ago. Measurements of natural neutrino emission have demonstrated that around half of the heat emanating from the Earth's core results from radioactive decay. However, it is not known if any of this results from fission chain-reactions.

Production of heavy elements

According to the theory, as the Universe cooled after the big bang it eventually became possible for common subatomic particles as we know them (neutrons, protons and electrons) to exist. The most common particles created in the big bang which are still easily observable to us today were protons and electrons (in equal numbers). The protons would eventually form hydrogen atoms. Almost all the neutrons created in the Big Bang were absorbed into helium-4 in the first three minutes after the Big Bang, and this helium accounts for most of the helium in the universe today (see Big Bang nucleosynthesis).

Some fraction of elements beyond helium were created in the Big Bang, as the protons and neutrons collided with each other (lithium, beryllium, and perhaps some boron), but all of the "heavier elements" (heavier than carbon, element number 6) that we see today, were created inside of stars during a series of fusion stages, such as the proton-proton chain, the CNO cycle and the triple-alpha process. Progressively heavier elements are created during the evolution of a star.

Since the binding energy per nucleon peaks around iron, energy is only released in fusion processes occurring below this point. Since the creation of heavier nuclei by fusion costs energy, nature resorts to the process of neutron capture. Neutrons (due to their lack of charge) are readily absorbed by a nucleus. The heavy elements are created by either a *slow* neutron capture process (the so-called *s* process) or by the *rapid*, or *r* process. The *s* process occurs in thermally pulsing stars (called AGB, or asymptotic giant branch stars) and takes hundreds to thousands of years to reach the heaviest elements of lead and bismuth. The *r* process is thought to occur in supernova explosions because the conditions of high temperature, high neutron flux and ejected matter are present. These stellar conditions make the successive neutron captures very fast, involving very neutron-rich species which then beta-decay to heavier elements, especially at the so-called waiting points that correspond to more stable nuclides with closed neutron shells

(magic numbers). The r process duration is typically in the range of a few seconds.

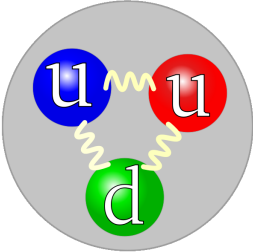
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- General Chemistry by Linus Pauling 1970 Dover Pub. ISBN 0-486-65622-5
- Introductory Nuclear Physics by Kenneth S. Krane Pub. Wiley
- Models of the Atomic Nucleus by N. Cook, Springer Verlag (2006), ISBN 3540285695

External links

- American Nuclear Society (<http://www.ans.org>)
- Boiling Water Reactor Plant, BWR Simulator Program (<http://www.acme-nuclear.com>)
- Annotated bibliography on nuclear physics from the Alsos Digital Library for Nuclear Issues (<http://alsos.wlu.edu/qsearch.aspx?browse=science/Nuclear+Physics>)
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- Nuclear Data Services - IAEA (<http://www-nds.iaea.org>)

Quark

Quark	
	
A proton, composed of two up quarks and one down quark. (The color assignment of individual quarks is not important, only that all three colors are present.)	
Composition:	Elementary particle
Particle statistics:	Fermionic
Generation:	1st, 2nd, 3rd
Interaction:	Electromagnetism, Gravitation, Strong, Weak
Symbol(s):	q
Antiparticle:	Antiquark (q)
Theorized:	Murray Gell-Mann (1964) George Zweig (1964)
Discovered:	SLAC (~1968)
Types:	6 (up, down, strange, charm, top, and bottom)
Electric charge:	$+\frac{2}{3}e, -\frac{1}{3}e$
Color charge:	Yes
Spin:	$\frac{1}{2}$

A **quark** (pronounced /'kwɔrk/ or English pronunciation: /'kwɔrk/) is an elementary particle and a fundamental constituent of matter. Quarks combine to form composite particles called hadrons, the most stable of which are protons and neutrons, the components of atomic nuclei.^[1] Due to a phenomenon known as *color confinement*, quarks are never found in isolation; they can only be found within hadrons.^[2] ^[3] For this reason, much of what is known about quarks has been drawn from observations of the hadrons themselves.

There are six types of quarks, known as *flavors*: up, down, charm, strange, top, and bottom.^[4] Up and down quarks have the lowest masses of all quarks. The heavier quarks rapidly change into up and down quarks through a process of particle decay: the transformation from a higher mass state to a lower mass state. Because of this, up and down quarks are generally stable and the most common in the universe, whereas charm, strange, top, and bottom quarks can only be produced in high energy collisions (such as those involving cosmic rays and in particle accelerators).

Quarks have various intrinsic properties, including electric charge, color charge, spin, and mass. Quarks are the only elementary particles in the Standard Model of particle physics to experience all four fundamental interactions, also known as *fundamental forces* (electromagnetism, gravitation, strong interaction, and weak interaction), as well as the only known particles whose electric charges are not integer multiples of the elementary charge. For every quark flavor there is a corresponding type of antiparticle, known as *antiquark*, that differs from the quark only in that some

of its properties have equal magnitude but opposite sign.

The quark model was independently proposed by physicists Murray Gell-Mann and George Zweig in 1964.^[5] Quarks were introduced as parts of an ordering scheme for hadrons, and there was little evidence for their physical existence until deep inelastic scattering experiments at SLAC in 1968.^[6] ^[7] All six flavors of quark have since been observed in accelerator experiments; the top quark, first observed at Fermilab in 1995, was the last to be discovered.^[5]

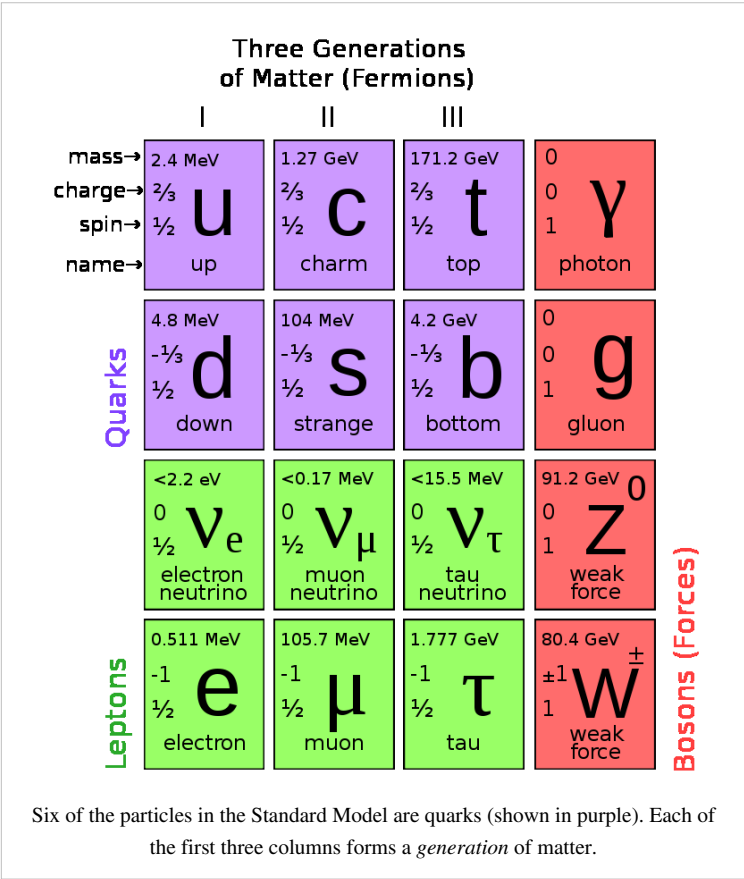
Classification

The Standard Model is the theoretical framework describing all the currently known elementary particles, as well as the unobserved^[8] Higgs boson.^[9] This model contains six flavors of quarks (q), named up (u), down (d), charm (c), strange (s), top (t), and bottom (b).^[4] Antiparticles of quarks are called *antiquarks*, and are denoted by a bar over the symbol for the corresponding quark, such as u for an up antiquark. As with antimatter in general, antiquarks have the same mass, mean lifetime, and spin as their respective quarks, but the electric charge and other charges have the opposite sign.^[10]

Quarks are spin- $\frac{1}{2}$ particles, implying that they are fermions according to the spin-statistics theorem. They are subject to the Pauli exclusion principle, which states that no two identical fermions can simultaneously occupy the same quantum state. This is in contrast to bosons (particles with integer spin), of which any number can be in the same state.^[11] Unlike leptons, quarks possess color charge, which causes them to engage in the strong interaction. The resulting attraction between different quarks causes the formation of composite particles known as *hadrons* (see "Strong interaction and color charge" below).

The quarks which determine the quantum numbers of hadrons are called *valence quarks*; apart from these, any hadron may contain an indefinite number of virtual (or *sea*) quarks, antiquarks, and gluons which do not influence its quantum numbers.^[12] There are two families of hadrons: baryons, with three valence quarks, and mesons, with a valence quark and an antiquark.^[13] The most common baryons are the proton and the neutron, the building blocks of the atomic nucleus.^[14] A great number of hadrons are known (see list of baryons and list of mesons), most of them differentiated by their quark content and the properties these constituent quarks confer. The existence of "exotic" hadrons with more valence quarks, such as tetraquarks (qqqq) and pentaquarks (qqqqq), has been conjectured^[15] but not proven.^[16] ^[15] ^[17]

Elementary fermions are grouped into three generations, each comprising two leptons and two quarks. The first generation includes up and down quarks, the second charm and strange quarks, and the third top and bottom quarks. All searches for a fourth generation of quarks and other elementary fermions have failed,^[18] and there is strong indirect evidence that no more than three generations exist.^[19] ^[20] Particles in higher generations generally have



greater mass and lesser stability, causing them to decay into lower-generation particles by means of weak interactions. Only first-generation (up and down) quarks occur commonly in nature. Heavier quarks can only be created in high-energy collisions (such as in those involving cosmic rays), and decay quickly; however, they are thought to have been present during the first fractions of a second after the Big Bang, when the universe was in an extremely hot and dense phase (the quark epoch). Studies of heavier quarks are conducted in artificially created conditions, such as in particle accelerators.^[21]

Having electric charge, mass, color charge, and flavor, quarks are the only known elementary particles that engage in all four fundamental interactions of contemporary physics: electromagnetism, gravitation, strong interaction, and weak interaction.^[14] Gravitation is too weak to be relevant to individual particle interactions except at extremes of energy (Planck energy) and distance scales (Planck distance). However, since no successful quantum theory of gravity exists, gravitation is not described by the Standard Model.

See the table of properties below for a more complete overview of the six quark flavors' properties.

History

The quark model was independently proposed by physicists Murray Gell-Mann^[22] and George Zweig^{[23] [24]} in 1964.^[5] The proposal came shortly after Gell-Mann's 1961 formulation of a particle classification system known as the *Eightfold Way*—or, in more technical terms, SU(3) flavor symmetry.^[25] Physicist Yuval Ne'eman had independently developed a scheme similar to the Eightfold Way in the same year.^{[26] [27]}

At the time of the quark theory's inception, the "particle zoo" included, amongst other particles, a multitude of hadrons. Gell-Mann and Zweig posited that they were not elementary particles, but were instead composed of combinations of quarks and antiquarks. Their model involved three flavors of quarks—up, down, and strange—to which they ascribed properties such as spin and electric charge.^{[22] [23] [24]} The initial reaction of the physics community to the proposal was mixed. There was particular contention about whether the quark was a physical entity or an abstraction used to explain concepts that were not properly understood at the time.^[28]



Murray Gell-Mann at TED in 2007.
Gell-Mann and George Zweig
proposed the quark model in 1964.

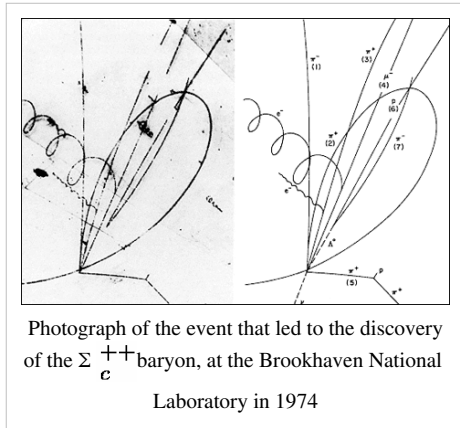
In less than a year, extensions to the Gell-Mann–Zweig model were proposed. Sheldon Lee Glashow and James Bjorken predicted the existence of a fourth flavor of quark, which they called *charm*. The addition was proposed because it allowed for a better description of the weak interaction (the mechanism that allows quarks to decay), equalized the number of known quarks with the number of known leptons, and implied a mass formula that correctly reproduced the masses of the known mesons.^[29]

In 1968, deep inelastic scattering experiments at the Stanford Linear Accelerator Center (SLAC) showed that the proton contained much smaller, point-like objects and was therefore not an elementary particle.^{[6] [7] [30]} Physicists were reluctant to identify these objects with quarks at the time, instead calling them "partons"—a term coined by Richard Feynman.^{[31] [32] [33]} The objects that were observed at the SLAC would later be identified as up and down quarks as the other flavors were discovered.^[34] Nevertheless, "parton" remains in use as a collective term for the constituents of hadrons (quarks, antiquarks, and gluons).

The strange quark's existence was indirectly validated by the SLAC's scattering experiments: not only was it a necessary component of Gell-Mann and Zweig's three-quark model, but it provided an explanation for the kaon (K) and pion (π) hadrons discovered in cosmic rays in 1947.^[35]

In a 1970 paper, Glashow, John Iliopoulos and Luciano Maiani presented further reasoning for the existence of the as-yet undiscovered charm quark.^{[36] [37]} The number of supposed quark flavors grew to the current six in 1973, when Makoto Kobayashi and Toshihide Maskawa noted that the experimental observation of CP violation^{[38] [39]}

could be explained if there were another pair of quarks.



Charm quarks were produced almost simultaneously by two teams in November 1974 (see November Revolution)—one at the SLAC under Burton Richter, and one at Brookhaven National Laboratory under Samuel Ting. The charm quarks were observed bound with charm antiquarks in mesons. The two parties had assigned the discovered meson two different symbols, J and ψ ; thus, it became formally known as the J/ψ meson. The discovery finally convinced the physics community of the quark model's validity.^[33]

In the following years a number of suggestions appeared for extending the quark model to six quarks. Of these, the 1975 paper by Haim Harari^[40] was the first to coin the terms *top* and *bottom* for the

additional quarks.^[41]

In 1977, the bottom quark was observed by a team at Fermilab led by Leon Lederman.^[42] ^[43] This was a strong indicator of the top quark's existence: without the top quark, the bottom quark would have been without a partner. However, it was not until 1995 that the top quark was finally observed, also by the CDF^[44] and DØ^[45] teams at Fermilab.^[5] It had a mass much greater than had been previously expected^[46]—almost as great as a gold atom.^[47]

Etymology

Gell-Mann originally named the quark after the sound made by ducks.^[48] For some time, he was undecided on an actual spelling for the term he intended to coin, until he found the word *quark* in James Joyce's book *Finnegans Wake*:

Three quarks for Muster Mark!
Sure he has not got much of a bark
And sure any he has it's all beside the mark.
—James Joyce, *Finnegans Wake*^[49]

Gell-Mann went into further detail regarding the name of the quark in his book, *The Quark and the Jaguar*.^[50]

In 1963, when I assigned the name "quark" to the fundamental constituents of the nucleon, I had the sound first, without the spelling, which could have been "kwork". Then, in one of my occasional perusals of *Finnegans Wake*, by James Joyce, I came across the word "quark" in the phrase "Three quarks for Muster Mark". Since "quark" (meaning, for one thing, the cry of the gull) was clearly intended to rhyme with "Mark", as well as "bark" and other such words, I had to find an excuse to pronounce it as "kwork". But the book represents the dream of a publican named Humphrey Chimpden Earwicker. Words in the text are typically drawn from several sources at once, like the "portmanteau" words in "Through the Looking-Glass". From time to time, phrases occur in the book that are partially determined by calls for drinks at the bar. I argued, therefore, that perhaps one of the multiple sources of the cry "Three quarks for Muster Mark" might be "Three quarts for Mister Mark", in which case the pronunciation "kwork" would not be totally unjustified. In any case, the number three fitted perfectly the way quarks occur in nature.

Zweig preferred the name *ace* for the particle he had theorized, but Gell-Mann's terminology came to prominence once the quark model had been commonly accepted.^[51]

The quark flavors were given their names for a number of reasons. The up and down quarks are named after the up and down components of isospin, which they carry.^[52] Strange quarks were given their name because they were discovered to be components of the strange particles discovered in cosmic rays years before the quark model was proposed; these particles were deemed "strange" because they had unusually long lifetimes.^[53] Glashow, who coproposed charm quark with Bjorken, is quoted as saying, "We called our construct the 'charmed quark', for we were fascinated and pleased by the symmetry it brought to the subnuclear world."^[54] The names "top" and "bottom", coined by Harari, were chosen because they are "logical partners for up and down quarks".^[40] ^[41] ^[53] In the past, top

and bottom quarks were sometimes referred to as "truth" and "beauty" respectively, but these names have mostly fallen out of use.^[55]

Properties

Electric charge

Quarks have fractional electric charge values—either $-\frac{1}{3}$ or $+\frac{2}{3}$ times the elementary charge, depending on flavor. Up, charm, and top quarks (collectively referred to as *up-type quarks*) have a charge of $+\frac{2}{3}$, while down, strange, and bottom quarks (*down-type quarks*) have $-\frac{1}{3}$. Antiquarks have the opposite charge to their corresponding quarks; up-type antiquarks have charges of $-\frac{2}{3}$ and down-type antiquarks have charges of $+\frac{1}{3}$. Since the electric charge of a hadron is the sum of the charges of the constituent quarks, all hadrons have integer charges: the combination of three quarks (baryons), three antiquarks (antibaryons), or a quark and an antiquark (mesons) always results in integer charges.^[56] For example, the hadron constituents of atomic nuclei, neutrons and protons, have charges of 0 and +1 respectively; the neutron is composed of two down quarks and one up quark, and the proton of two up quarks and one down quark.^[14]

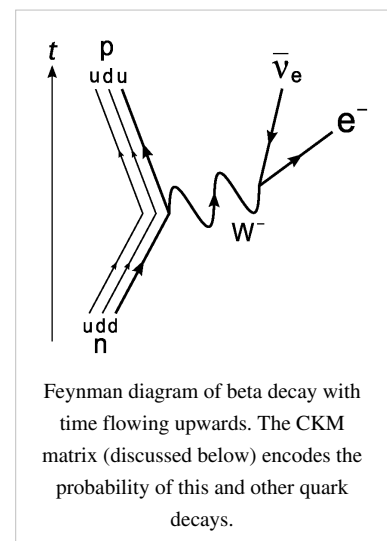
Spin

Spin is an intrinsic property of elementary particles, and its direction is an important degree of freedom. It is sometimes visualized as the rotation of an object around its own axis (hence the name "spin"), though this notion is somewhat misguided at subatomic scales because elementary particles are believed to be point-like.^[57]

Spin can be represented by a vector whose length is measured in units of the reduced Planck constant $\hbar$ (pronounced "h bar"). For quarks, a measurement of the spin vector component along any axis can only yield the values $+\hbar/2$ or $-\hbar/2$; for this reason quarks are classified as spin- $\frac{1}{2}$ particles.^[58] The component of spin along a given axis—by convention the z axis—is often denoted by an up arrow $\uparrow$ for the value $+\frac{1}{2}$ and down arrow $\downarrow$ for the value $-\frac{1}{2}$, placed after the symbol for flavor. For example, an up quark with a spin of $+\frac{1}{2}$ along the z axis is denoted by $u\uparrow$.^[59]

Weak interaction

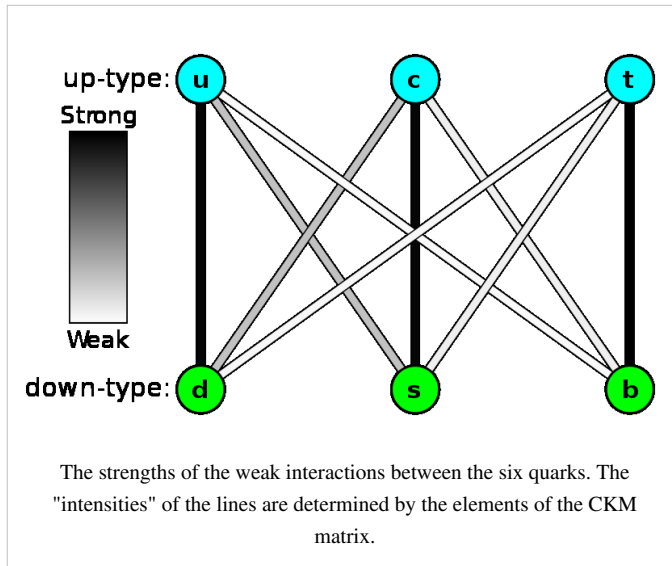
A quark of one flavor can transform into a quark of another flavor only through the weak interaction, one of the four fundamental interactions in particle physics. By absorbing or emitting a W boson, any up-type quark (up, charm, and top quarks) can change into any down-type quark (down, strange, and bottom quarks) and vice versa. This flavor transformation mechanism causes the radioactive process of beta decay, in which a neutron (n) "splits" into a proton (p), an electron (e^-) and an electron antineutrino ($\bar{\nu}_e$) (see picture). This occurs when one of the down quarks in the neutron (udd) decays into an up quark by emitting a virtual W^- boson, transforming the neutron into a proton (uud). The W^- boson then decays into an electron and an electron antineutrino.^[60]



$$n \rightarrow p + e^- + \bar{\nu}_e \quad (\text{Beta decay, hadron notation})$$

$$udd \rightarrow uud + e^- + \bar{\nu}_e \quad (\text{Beta decay, quark notation})$$

Both beta decay and the inverse process of *inverse beta decay* are routinely used in medical applications such as positron emission tomography (PET) and in high-energy experiments such as neutrino detection.



While the process of flavor transformation is the same for all quarks, each quark has a preference to transform into the quark of its own generation. The relative tendencies of all flavor transformations are described by a mathematical table, called the Cabibbo–Kobayashi–Maskawa matrix (CKM matrix). The approximate magnitudes of the entries of the CKM matrix are:^[61]

$$\begin{bmatrix} |V_{ud}| & |V_{us}| & |V_{ub}| \\ |V_{cd}| & |V_{cs}| & |V_{cb}| \\ |V_{td}| & |V_{ts}| & |V_{tb}| \end{bmatrix} \approx \begin{bmatrix} 0.974 & 0.225 & 0.003 \\ 0.225 & 0.973 & 0.041 \\ 0.009 & 0.040 & 0.999 \end{bmatrix},$$

where V_{ij} represents the tendency of a quark of flavor i to change into a quark of flavor j (or vice versa).^[62]

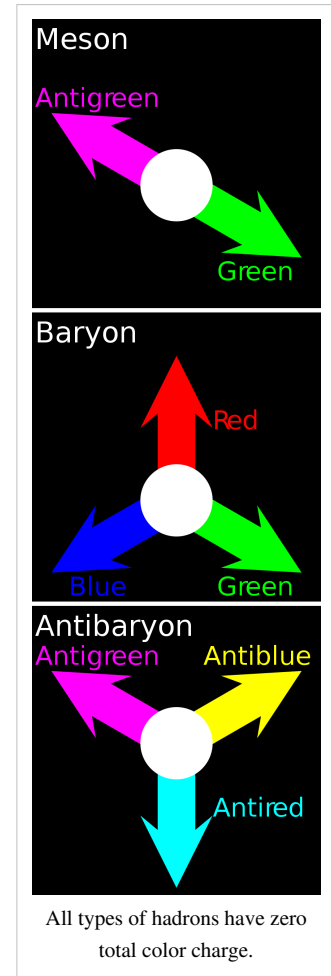
There exists an equivalent weak interaction matrix for leptons (right side of the W boson on the above beta decay diagram), called the Pontecorvo–Maki–Nakagawa–Sakata matrix (PMNS matrix).^[63] Together, the CKM and PMNS matrices describe all flavor transformations, but the links between the two are not yet clear.^[64]

Strong interaction and color charge

Quarks possess a property called *color charge*. There are three types of color charge, arbitrarily labeled *blue*, *green*, and *red*.^[65] Each of them is complemented by an anticolor—*antiblu*e, *antigreen*, and *antired*. Every quark carries a color, while every antiquark carries an anticolor.^[66]

The system of attraction and repulsion between quarks charged with different combinations of the three colors is called strong interaction, which is mediated by force carrying particles known as *gluons*; this is discussed at length below. The theory that describes strong interactions is called quantum chromodynamics (QCD). A quark charged with one color value can form a bound system with an antiquark carrying the corresponding anticolor; three (anti)quarks, one of each (anti)color, will similarly be bound together. The result of two attracting quarks will be color neutrality: a quark with color charge ξ plus an antiquark with color charge $-\xi$ will result in a color charge of 0 (or "white" color) and the formation of a meson. Analogous to the additive color model in basic optics, the combination of three quarks or three antiquarks, each with different color charges, will result in the same "white" color charge and the formation of a baryon or antibaryon.^[67]

In modern particle physics, gauge symmetries—a kind of symmetry group—relate interactions between particles (see gauge theories). Color SU(3) (commonly abbreviated to SU(3)_c) is the gauge symmetry that relates the color charge in quarks and is the defining symmetry for quantum chromodynamics.^[68] Just as the laws of physics are independent of which directions in space are designated *x*, *y*, and *z*, and remain unchanged if the coordinate axes are rotated to a new orientation, the physics of quantum chromodynamics is independent of which directions in three-dimensional color space are identified as blue, red, and green. SU(3)_c color transformations correspond to "rotations" in color space (which, mathematically speaking, is a complex space). Every quark flavor *f*, each with subtypes f_B , f_G , f_R corresponding to the quark colors,^[69] forms a triplet: a three-component quantum field which transforms under the fundamental representation of SU(3)_c.^[70] The requirement that SU(3)_c should be local—that is, that its transformations be allowed to vary with space and time—determines the properties of the strong interaction, in particular the existence of eight gluon types to act as its force carriers.^{[68] [71]}



Mass

Two terms are used in referring to a quark's mass: *current quark mass* refers to the mass of a quark by itself, while *constituent quark mass* refers to the current quark mass plus the mass of the gluon particle field surrounding the quark.^[72] These masses typically have very different values. Most of a hadron's mass comes from the gluons that bind the constituent quarks together, rather than from the quarks themselves. While gluons are inherently massless, they possess energy—more specifically, quantum chromodynamics binding energy (QCBE)—and it is this that contributes so greatly to the overall mass of the hadron (see mass in special relativity). For example, a proton has a mass of approximately $938 \text{ MeV}/c^2$, of which the rest mass of its three valence quarks only contributes about $11 \text{ MeV}/c^2$; much of the remainder can be attributed to the gluons' QCBE.^{[73] [74]}

The Standard Model posits that elementary particles derive their masses from the Higgs mechanism, which is related to the unobserved Higgs boson. Physicists hope that further research into the reasons for the top quark's large mass, which was found to be approximately equal to that of a gold nucleus ($\sim 171 \text{ GeV}/c^2$),^{[73] [75]} might reveal more about the origin of the mass of quarks and other elementary particles.^[76]

Table of properties

The following table summarizes the key properties of the six quarks. Flavor quantum numbers (isospin (I_3), charm (C), strangeness (S , not to be confused with spin), topness (T), and bottomness (B')) are assigned to certain quark flavors, and denote qualities of quark-based systems and hadrons. The baryon number (B) is $+\frac{1}{3}$ for all quarks, as baryons are made of three quarks. For antiquarks, the electric charge (Q) and all flavor quantum numbers (B , I_3 , C , S , T , and B') are of opposite sign. Mass and total angular momentum (J ; equal to spin for point particles) do not change sign for the antiquarks.

Quark flavor properties^[73]

Name	Symbol	Mass (MeV/c ²)*	J	B	Q	I_3	C	S	T	B'	Antiparticle	Antiparticle symbol
First generation												
Up	u	1.7 to 3.3	$\frac{1}{2}$	$+\frac{1}{3}$	$+\frac{2}{3}$	$+\frac{1}{2}$	0	0	0	0	Antiup	u
Down	d	4.1 to 5.8	$\frac{1}{2}$	$+\frac{1}{3}$	$-\frac{1}{3}$	$-\frac{1}{2}$	0	0	0	0	Antidown	d
Second generation												
Charm	c	1270^{+70}_{-90}	$\frac{1}{2}$	$+\frac{1}{3}$	$+\frac{2}{3}$	0	+1	0	0	0	Anticharm	c
Strange	s	101^{+29}_{-21}	$\frac{1}{2}$	$+\frac{1}{3}$	$-\frac{1}{3}$	0	0	−1	0	0	Antistrange	s
Third generation												
Top	t	$172000 \pm 900 \pm 1,300$	$\frac{1}{2}$	$+\frac{1}{3}$	$+\frac{2}{3}$	0	0	0	+1	0	Antitop	t
Bottom	b	4190^{+180}_{-60}	$\frac{1}{2}$	$+\frac{1}{3}$	$-\frac{1}{3}$	0	0	0	0	−1	Antibottom	b

J = total angular momentum, B = baryon number, Q = electric charge, I_3 = isospin, C = charm, S = strangeness, T = topness, B' = bottomness.
* Notation such as 4190^{+180}_{-60} denotes measurement uncertainty. In the case of the top quark, the first uncertainty is statistical in nature, and the second is systematic.

Interacting quarks

As described by quantum chromodynamics, the strong interaction between quarks is mediated by gluons, massless vector gauge bosons. Each gluon carries one color charge and one anticolor charge. In the standard framework of particle interactions (part of a more general formulation known as perturbation theory), gluons are constantly exchanged between quarks through a virtual emission and absorption process. When a gluon is transferred between quarks, a color change occurs in both; for example, if a red quark emits a red–antigreen gluon, it becomes green, and if a green quark absorbs a red–antigreen gluon, it becomes red. Therefore, while each quark's color constantly changes, their strong interaction is preserved.^{[77] [78] [79]}

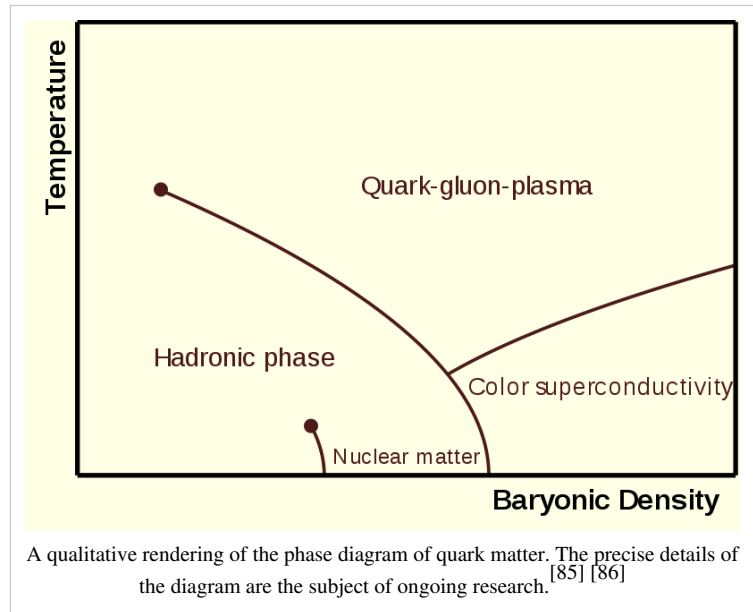
Since gluons carry color charge, they themselves are able to emit and absorb other gluons. This causes *asymptotic freedom*: as quarks come closer to each other, the chromodynamic binding force between them weakens.^[80] Conversely, as the distance between quarks increases, the binding force strengthens. The color field becomes stressed, much as an elastic band is stressed when stretched, and more gluons of appropriate color are spontaneously created to strengthen the field. Above a certain energy threshold, pairs of quarks and antiquarks are created. These pairs bind with the quarks being separated, causing new hadrons to form. This phenomenon is known as *color confinement*: quarks never appear in isolation.^{[78] [81]} This process of hadronization occurs before quarks formed in a high energy collision are able to interact in any other way. The only exception is the top quark, which may decay before it hadronizes.^[82]

Sea quarks

Hadrons, along with the *valence quarks* (q_v) that contribute to their quantum numbers, contain virtual quark–antiquark ($q\bar{q}$) pairs known as *sea quarks* (q_s). Sea quarks form when a gluon of the hadron's color field splits; this process also works in reverse in that the annihilation of two sea quarks produces a gluon. The result is a constant flux of gluon splits and creation colloquially known as "the sea".^[83] Sea quarks are much less stable than their valence counterparts, and they typically annihilate each other within the interior of the hadron. Despite this, sea quarks can hadronize into baryonic or mesonic particles under certain circumstances.^[84]

Other phases of quark matter

Under sufficiently extreme conditions, quarks may become deconfined and exist as free particles. In the course of asymptotic freedom, the strong interaction becomes weaker at higher temperatures. Eventually, color confinement would be lost and an extremely hot plasma of freely moving quarks and gluons would be formed. This theoretical phase of matter is called quark–gluon plasma.^[87] The exact conditions needed to give rise to this state are unknown and have been the subject of a great deal of speculation and experimentation. A recent estimate puts the needed temperature at $1.90 \pm 0.02 \times 10^{12}$ kelvins.^[88] While a state of entirely free quarks and gluons has never been achieved (despite numerous attempts by CERN in the 1980s and 1990s),^[89] recent experiments at the Relativistic Heavy Ion Collider have yielded evidence for liquid-like quark matter exhibiting "nearly perfect" fluid motion.^[90]



The quark–gluon plasma would be characterized by a great increase in the number of heavier quark pairs in relation to the number of up and down quark pairs. It is believed that in the period prior to 10^{-6} seconds after the Big Bang (the quark epoch), the universe was filled with quark–gluon plasma, as the temperature was too high for hadrons to be stable.^[91]

Given sufficiently high baryon densities and relatively low temperatures—possibly comparable to those found in neutron stars—quark matter is expected to degenerate into a Fermi liquid of weakly interacting quarks. This liquid would be characterized by a condensation of colored quark Cooper pairs, thereby breaking the local $SU(3)_c$ symmetry. Because quark Cooper pairs harbor color charge, such a phase of quark matter would be color superconductive; that is, color charge would be able to pass through it with no resistance.^[92]

See also

- Color–flavor locking
- Quarkonium – Mesons made of a quark and antiquark of the same flavor
- Preons – Hypothetical particles which were once postulated to be subcomponents of quarks and leptons
- Quark–lepton complementarity – Possible fundamental relation between quarks and leptons
- Quark star – A hypothetical degenerate neutron star with extreme density

Notes

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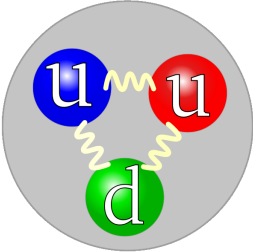
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External links

- 1969 Physics Nobel Prize lecture by Murray Gell-Mann (http://nobelprize.org/nobel_prizes/physics/laureates/1969/index.html)
 - 1976 Physics Nobel Prize lecture by Burton Richter (http://nobelprize.org/nobel_prizes/physics/laureates/1976/richter-lecture.html)
 - 1976 Physics Nobel Prize lecture by Samuel C.C. Ting (http://nobelprize.org/nobel_prizes/physics/laureates/1976/ting-lecture.html)
 - 2008 Physics Nobel Prize lecture by Makoto Kobayashi (http://nobelprize.org/nobel_prizes/physics/laureates/2008/kobayashi-lecture.html)
 - 2008 Physics Nobel Prize lecture by Toshihide Maskawa (http://nobelprize.org/nobel_prizes/physics/laureates/2008/maskawa-lecture.html)
 - The Top Quark And The Higgs Particle by T.A. Heppenheimer (<http://books.nap.edu/openbook.php?isbn=0309048931&page=236>) – A description of CERN's experiment to count the families of quarks.
-

Proton

Proton	
	
The quark structure of the proton. (The color assignment of individual quarks is not important, only that all three colors are present.)	
Classification:	Baryon
Composition:	2 up quarks, 1 down quark
Particle statistics:	Fermionic
Group:	Hadron
Interaction:	Gravity, Electromagnetic, Weak, Strong
Symbol(s):	p, p ⁺ , N ⁺
Antiparticle:	Antiproton
Theorized:	William Prout (1815)
Discovered:	Ernest Rutherford (1919)
Mass:	1.672621637(83) × 10 ⁻²⁷ kg 938.272013(23) MeV/c ² 1.00727646677(10) u ^[1]
Mean lifetime:	>2.1 × 10 ²⁹ yr (stable)
Electric charge:	+1 e 1.602176487(40) × 10 ⁻¹⁹ C ^[1]
Charge radius:	0.877 fm ^[1]
Electric dipole moment:	<5.4 × 10 ⁻²⁴ e·cm
Electric polarizability:	1.20(6) × 10 ⁻³ fm ³
Magnetic moment:	2.792847351(28) μ _N
Magnetic polarizability:	1.9(5) × 10 ⁻⁴ fm ³
Spin:	1/2
Isospin:	1/2
Parity:	+1
Condensed:	I(J ^P) = 1/2(1/2 ⁺)

The **proton** is a subatomic particle with an electric charge of +1 elementary charge. One or more protons are present in the nucleus of each atom, along with neutrons. The proton is also stable by itself and has a second identity as the hydrogen ion, H^+ . The proton is composed of three fundamental particles: two up quarks and one down quark.^[2]

Description

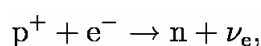
Protons are spin- $\frac{1}{2}$ fermions and are composed of three quarks,^[3] making them baryons (a sub-type of hadrons). The two up quarks and one down quark of the proton are held together by the strong force, mediated by gluons.^[2] The proton has an approximately exponentially decaying positive charge distribution with a mean square radius of about 0.8 fm.^[4]

Protons and neutrons are both nucleons, which may be bound by the nuclear force into atomic nuclei. The nucleus of the most common isotope of the hydrogen atom is a lone proton. The nuclei of the heavy hydrogen isotopes deuterium and tritium contain one proton bound to one and two neutrons, respectively. All other types of atoms are composed of two or more protons and various numbers of neutrons. The number of protons in the nucleus determines the chemical properties of the atom and thus which chemical element is represented; it is the number of both neutrons and protons in a nuclide which determine the particular isotope of an element.

Stability

Protons are stable with an empirically observed half-life of at least 6.6×10^{33} yr.^[5] Although experiments so far have only resulted in a lower limit of 10^{33} years for the proton's lifetime, Grand unified theories generally predict that proton decay should take place. In other words, proton decay has never been witnessed and the experimental lower bound on the mean proton lifetime (2.1×10^{29} yr) is given by the Sudbury Neutrino Observatory.^[6]

However, protons are known to transform into neutrons through the process of electron capture (also called inverse beta decay). For free protons this process does not occur spontaneously but only when energy is supplied. The equation is:



where p is a proton, e is an electron, n is a neutron, and ν_e is an electron neutrino.

The process is reversible; neutrons can convert back to protons through beta decay, a common form of radioactive decay. In fact, a free neutron decays this way with a mean lifetime of about 15 minutes.

Quarks and the mass of the proton

In quantum chromodynamics, the modern theory of the nuclear force, most of the mass of the proton and the neutron is explained by special relativity. The mass of the proton is about eighty times greater than the sum of the rest masses of the quarks that make it up, while the gluons have zero rest mass. The extra energy of the quarks and gluons in a region within a proton, as compared to the energy of the quarks and gluons in the QCD vacuum, accounts for over 98% of the mass.

The internal dynamics of the proton are complicated, because they are determined by the quarks exchanging gluons, and interacting with various vacuum condensates. Lattice QCD provides a way of calculating the mass of the proton directly from the theory to any accuracy, in principle. The most recent calculations^[7] ^[8] claim that the mass is determined to better than 4% accuracy, arguably accurate to 1% (see Figure S5 in Dürr *et al.*^[8]). These claims are still controversial, because the calculations cannot yet be done with quarks as light as they are in the real world. This means that the predictions are found by a process of extrapolation, which can introduce systematic errors.^[9] It is hard to tell whether these errors are controlled properly, because the quantities that are compared to experiment are the masses of the hadrons, which are known in advance.

These recent calculations are performed by massive supercomputers, and, as noted by Boffi and Pasquini: “a detailed description of the nucleon structure is still missing because ... long-distance behavior requires a nonperturbative and/or numerical treatment...”^[10] More conceptual approaches to the structure of the proton are: the topological soliton approach originally due to Tony Skyrme and the more accurate AdS/QCD approach which extends it to include a string theory of gluons, various QCD inspired models like the bag model and the constituent quark model, which were popular in the 1980s, and the SVZ sum rules which allow for rough approximate mass calculations. These methods don't have the same accuracy as the more brute force lattice QCD methods, at least not yet.

Charge Radius

The internationally-accepted value of the proton's charge radius is 0.8768 femtometers. This value is based on measurements involving a proton and an electron.

However since July 5, 2010 an international research team has been able to make measurements involving a proton and a negatively-charged muon. After a long and careful analysis of those measurements the team concluded that the root-mean-square charge radius of a proton is "0.84184(67) fm, which differs by 5.0 standard deviations from the CODATA value of 0.8768(69) fm."^[11]

The international research team that obtained this result at the Paul-Scherrer-Institut (PSI) in Villigen (Switzerland) includes scientists from the Max Planck Institute of Quantum Optics (MPQ) in Garching, the Ludwig-Maximilians-Universität (LMU) Munich and the Institut für Strahlwerkzeuge (IFWS) of the Universität Stuttgart (both from Germany), and the University of Coimbra, Portugal.^{[12] [13]} They are now attempting to explain the discrepancy, and re-examining the results of both previous high-precision measurements and complicated calculations. If no errors are found in the measurements or calculations, it could be necessary to re-examine the world's most precise and best-tested fundamental theory: quantum electrodynamics.^[14]

The Proton in Chemistry

Atomic number

In chemistry the number of protons in the nucleus of an atom is known as the atomic number, which determines the chemical element to which the atom belongs. For example, the atomic number of chlorine is 17; this means that each chlorine atom has 17 protons and that all atoms with 17 protons are chlorine atoms. The chemical properties of each atom are determined by the number of (negatively charged) electrons, which for neutral atoms is equal to the number of (positive) protons so that the total charge is zero. For example, a neutral chlorine atom has 17 protons and 17 electrons, while a negative Cl^- ion has 17 protons and 18 electrons for a total charge of -1 .

All atoms of a given element are not necessarily identical, however, as the number of neutrons may vary to form different isotopes, and energy levels may differ forming different isomers. For example, there are two stable isotopes of chlorine: $^{35}_{17}\text{Cl}$ and $^{37}_{17}\text{Cl}$.

Hydrogen as proton

Since the atomic number of hydrogen is 1, a positive hydrogen ion (H^+) has no electrons and corresponds to a bare nucleus with 1 proton (and 0 neutrons for the most abundant isotope ^1_1H). In chemistry and biology therefore, the word "proton" is commonly used as a synonym for hydrogen ion (H^+) or hydrogen nucleus in several contexts:

1. The transfer of H^+ in an acid-base reaction is referred to as "proton transfer". The acid is referred to as a proton donor and the base as a proton acceptor.
2. The hydronium ion (H_3O^+) in aqueous solution corresponds to a hydrated hydrogen ion. Often the water molecule is ignored and the ion written as simply $\text{H}^+(\text{aq})$ or just H^+ , and referred to as a "proton". This is the usual meaning in biochemistry, as in the term proton pump which refers to a protein or enzyme which controls the

movement of H^+ ions across cell membranes.

3. Proton NMR refers to the observation of hydrogen nuclei in (mostly organic) molecules by nuclear magnetic resonance. This method uses the spin of the proton, which has the value one-half.

History

The concept of a hydrogen-like particle as a constituent of other atoms was developed over a long period. As early as 1815, William Prout proposed that all atoms are composed of hydrogen atoms, based on a simplistic interpretation of early values of atomic weights (see Prout's hypothesis), which was disproved when more accurate values were measured.

In 1886 Eugen Goldstein discovered canal rays (also known as anode rays) and showed that they were positively charged particles (ions) produced from gases. However, since particles from different gases had different values of charge-to-mass ratio (e/m), they could not be identified with a single particle, unlike the negative electrons discovered by J. J. Thomson.

Following the discovery of the atomic nucleus by Ernest Rutherford in 1911, Antonius van den Broek proposed that the place of each element in the periodic table (its atomic number) is equal to its nuclear charge. This was confirmed experimentally by Henry Moseley in 1913 using X-ray spectra. In 1919 Rutherford proved that the hydrogen nucleus is present in other nuclei, a result usually described as the discovery of the proton.^[15] He noticed that when alpha particles were shot into nitrogen gas, his scintillation detectors showed the signatures of hydrogen nuclei. Rutherford determined that this hydrogen could only have come from the nitrogen, and therefore nitrogen must contain hydrogen nuclei. The hydrogen nucleus is therefore present in other nuclei as an elementary particle, which Rutherford named the proton, after the neuter singular of the Greek word for "first", $\pi\rho\omega\tau\omicron\nu$.

Exposure

The Apollo Lunar Surface Experiments Packages (ALSEP) determined that more than 95% of the particles in the solar wind are electrons and protons, in approximately equal numbers.^{[16] [17]}

Because the Solar Wind Spectrometer made continuous measurements, it was possible to measure how the Earth's magnetic field affects arriving solar wind particles. For about two-thirds of each orbit, the Moon is outside of the Earth's magnetic field. At these times, a typical proton density was 10 to 20 per cubic centimeter, with most protons having velocities between 400 and 650 kilometers per second. For about five days of each month, the Moon is inside the Earth's geomagnetic tail, and typically no solar wind particles were detectable. For the remainder of each lunar orbit, the Moon is in a transitional region known as the magnetosheath, where the Earth's magnetic field affects the solar wind but does not completely exclude it. In this region, the particle flux is reduced, with typical proton velocities of 250 to 450 kilometers per second. During the lunar night, the spectrometer was shielded from the solar wind by the Moon and no solar wind particles were measured.^[16]

Research has been performed on the dose-rate effects of protons, as typically found in space travel, on human health.^{[17] [18]} More specifically, there are hopes to identify what specific chromosomes are damaged, and to define the damage, during cancer development from proton exposure.^[17] Another study looks into determining "the effects of exposure to proton irradiation on neurochemical and behavioral endpoints, including dopaminergic functioning, amphetamine-induced conditioned taste aversion learning, and spatial learning and memory as measured by the Morris water maze."^[18] Electrical charging of a spacecraft due to interplanetary proton bombardment has also been proposed for study.^[19] There are many more studies which pertain to space travel, including galactic cosmic rays and their possible health effects, and solar proton event exposure.

The American Biostack and Soviet Biorack space travel experiments have demonstrated the severity of molecular damage induced by heavy ions on micro organisms including *Artemia* cysts.^[20]

Antiproton

CPT-symmetry puts strong constraints on the relative properties of particles and antiparticles and, therefore, is open to stringent tests. For example, the charges of the proton and antiproton must sum to exactly zero. This equality has been tested to one part in 10^8 . The equality of their masses has also been tested to better than one part in 10^8 . By holding antiprotons in a Penning trap, the equality of the charge to mass ratio of the proton and the antiproton has been tested to one part in 6×10^9 .^[21] The magnetic moment of the antiproton has been measured with error of 8×10^{-3} nuclear Bohr magnetons, and is found to be equal and opposite to that of the proton.

See also

- Electron
- Fermion field
- Hydrogen
- Hydron (chemistry)
- List of particles
- Neutron
- Particle physics
- Proton decay
- Proton-proton chain reaction
- Proton therapy
- Quark model
- Subatomic particle

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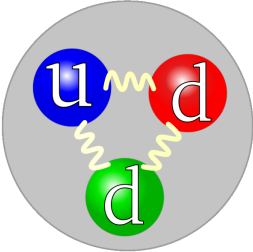
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External links

- Particle Data Group (<http://pdg.lbl.gov>)
- Large Hadron Collider (<http://www.cern.ch/lhc/>)

Neutron

Neutron	
	
The quark structure of the neutron. (The color assignment of individual quarks is not important, only that all three colors are present.)	
Classification:	Baryon
Composition:	1 up quark, 2 down quarks
Particle statistics:	Fermionic
Group:	Hadron
Interaction:	Gravity, Weak, Strong
Symbol(s):	n, n ⁰ , N ⁰
Antiparticle:	Antineutron
Theorized:	Ernest Rutherford ^[1] (1920)
Discovered:	James Chadwick ^[1] (1932)
Mass:	1.67492729(28) × 10 ^{−27} kg 939.565560(81) MeV/c ² 1.0086649156(6) u ^[2]
Mean lifetime:	885.7(8) s (free)
Electric charge:	0 e 0 C
Electric dipole moment:	<2.9 × 10 ^{−26} e·cm
Electric polarizability:	1.16(15) × 10 ^{−3} fm ³
Magnetic moment:	−1.9130427(5) μ _N
Magnetic polarizability:	3.7(20) × 10 ^{−4} fm ³
Spin:	1/2
Isospin:	1/2
Parity:	+1
Condensed:	I(J ^P) = 1/2(1/2 ⁺)

The **neutron** is a subatomic particle with no net electric charge and a mass slightly larger than that of a proton. With the exception of hydrogen, nuclei of atoms consist of protons and neutrons, which are therefore collectively referred

to as nucleons. The number of protons in a nucleus is the atomic number and defines the type of element the atom forms. The number of neutrons is the neutron number and determines the isotope of an element. For example, the abundant carbon-12 isotope has 6 protons and 6 neutrons, while the very rare radioactive carbon-14 isotope has 6 protons and 8 neutrons.

While bound neutrons in stable nuclei are stable, free neutrons are unstable; they undergo beta decay with a mean lifetime of just under 15 minutes (885.7 ± 0.8 s).^[2] Free neutrons are produced in nuclear fission and fusion. Dedicated neutron sources like research reactors and spallation sources produce free neutrons for use in irradiation and in neutron scattering experiments. Even though it is not a chemical element, the free neutron is sometimes included in tables of nuclides.^[3] It is then considered to have an atomic number of zero and a mass number of one, and is sometimes referred to as neutronium.

The neutron has been the key to nuclear power production. After the neutron was discovered in 1932, it was realized in 1933 that it might mediate a nuclear chain reaction. In the 1930s, neutrons were used to produce many different types of nuclear transmutations. When nuclear fission was discovered in 1938, it was soon realized that this might be the mechanism to produce the neutrons for the chain reaction, if the process also produced neutrons, and this was proven in 1939, making the path to nuclear power production evident. These events and findings led directly to the first man-made nuclear chain reaction which was self-sustaining (1942) and to the first nuclear weapons in 1945.

Discovery

In 1920, Ernest Rutherford conceptualised the possible existence of the neutron. In particular, Rutherford considered that the disparity found between the atomic number of an atom and its atomic mass could be explained by the existence of a neutrally charged particle within the atomic nucleus.

In 1930 Viktor Ambartsumian and Dmitri Ivanenko in USSR found that contrary to the prevailing opinion of the time nucleus can not consist of protons and electrons. They proved that some neutral particles must be present besides the protons.^[4]

In 1931, Walther Bothe and Herbert Becker in Germany found that if the very energetic alpha particles emitted from polonium fell on certain light elements, specifically beryllium, boron, or lithium, an unusually penetrating radiation was produced. At first this radiation was thought to be gamma radiation, although it was more penetrating than any gamma rays known, and the details of experimental results were very difficult to interpret on this basis. The next important contribution was reported in 1932 by Irène Joliot-Curie and Frédéric Joliot in Paris. They showed that if this unknown radiation fell on paraffin, or any other hydrogen-containing compound, it ejected protons of very high energy. This was not in itself inconsistent with the assumed gamma ray nature of the new radiation, but detailed quantitative analysis of the data became increasingly difficult to reconcile with such a hypothesis.

In 1932, James Chadwick performed a series of experiments at the University of Cambridge, showing that the gamma ray hypothesis was untenable. He suggested that the new radiation consisted of uncharged particles of approximately the mass of the proton, and he performed a series of experiments verifying his suggestion.^[5] These uncharged particles were called *neutrons*, apparently from the Latin root for *neutral* and the Greek ending *-on* (by imitation of *electron* and *proton*).

The discovery of the neutron explained a puzzle involving the spin of the nitrogen-14 nucleus, which had been experimentally measured to be $1 \hbar$. It was known that atomic nuclei usually had about half as many positive charges as if they were composed completely of protons, and in existing models this was often explained by proposing that nuclei also contained some "nuclear electrons" to neutralize the excess charge. Thus, nitrogen-14 would be composed of 14 protons and 7 electrons to give it a charge of +7 but a mass of 14 atomic mass units. However, it was also known that both protons and electrons carried an intrinsic spin of $\frac{1}{2} \hbar$, and there was no way to arrange an odd number (21) of spins $\pm \frac{1}{2} \hbar$ to give a spin of $1 \hbar$. Instead, when nitrogen-14 was proposed to consist of 3 pairs of protons and neutrons, with an additional unpaired neutron and proton each contributing a spin of $\frac{1}{2} \hbar$ in the same direction for a total spin of $1 \hbar$, the model became viable. Soon, nuclear neutrons were used to naturally explain spin

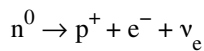
differences in many different nuclides in the same way, and the neutron as a basic structural unit of atomic nuclei was accepted.

Intrinsic properties

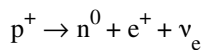
Stability and beta decay

Under the Standard Model of particle physics, because the neutron consists of three quarks, the only possible decay mode without a change of baryon number is for one of the quarks to change flavour via the weak interaction. The neutron consists of two down quarks with charge $-\frac{1}{3}e$ and one up quark with charge $+\frac{2}{3}e$, and the decay of one of the down quarks into a lighter up quark can be achieved by the emission of a W boson. By this means the neutron decays into a proton (which contains one down and two up quarks), an electron, and an electron antineutrino.

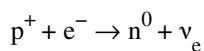
Outside the nucleus, free neutrons are unstable and have a mean lifetime of 885.7 ± 0.8 s (about 14 minutes, 46 seconds); therefore the half-life for this process (which differs from the mean lifetime by a factor of $\ln(2) = 0.693$) is 613.9 ± 0.8 s (about 10 minutes, 14 seconds).^[2] Free neutrons decay by emission of an electron and an electron antineutrino to become a proton, a process known as beta decay:^[6]



Neutrons in unstable nuclei can also decay in this manner. However, inside a nucleus, protons can also transform into a neutron via inverse beta decay. This transformation occurs by emission of a antielectron (also called positron) and a neutrino:



The transformation of a proton to a neutron inside of a nucleus is also possible through electron capture:

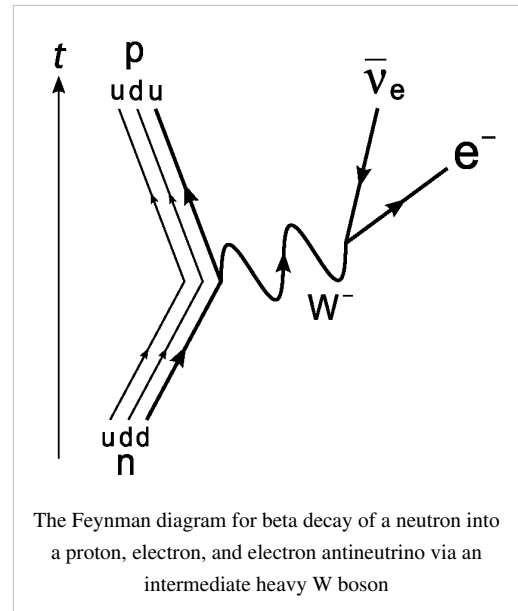


Positron capture by neutrons in nuclei that contain an excess of neutrons is also possible, but is hindered because positrons are repelled by the nucleus, and quickly annihilate when they encounter electrons.

When bound inside of a nucleus, the instability of a single neutron to beta decay is balanced against the instability that would be acquired by the nucleus as a whole if an additional proton were to participate in repulsive interactions with the other protons that are already present in the nucleus. As such, although free neutrons are unstable, bound neutrons are not necessarily so. The same reasoning explains why protons, which are stable in empty space, may transform into neutrons when bound inside of a nucleus.

Electric dipole moment

The Standard Model of particle physics predicts a tiny separation of positive and negative charge within the neutron leading to a permanent electric dipole moment.^[7] The predicted value is, however, well below the current sensitivity of experiments. From several unsolved puzzles in particle physics, it is clear that the Standard Model is not the final and full description of all particles and their interactions. New theories going beyond the Standard Model generally lead to much larger predictions for the electric dipole moment of the neutron. Currently, there are at least four experiments trying to measure for the first time a finite neutron electric dipole moment, including:



- [8] Cryogenic neutron EDM experiment being set up at the Institut Laue-Langevin
- [9] nEDM experiment under construction at the new UCN source at the Paul Scherrer Institute
- [10] nEDM experiment being envisaged at the Spallation Neutron Source
- [11] nEDM experiment being built at the Institut Laue-Langevin

Magnetic moment

Magnetic moment of a neutron is nonzero, unexpected from an electrically neutral particle. This indicates that neutron is a composite particle.

Anti-neutron

The antineutron is the antiparticle of the neutron. It was discovered by Bruce Cork in the year 1956, a year after the antiproton was discovered. CPT-symmetry puts strong constraints on the relative properties of particles and antiparticles, so studying antineutrons yields provide stringent tests on CPT-symmetry. The fractional difference in the masses of the neutron and antineutron is $9 \pm 5 \times 10^{-5}$. Since the difference is only about 2 standard deviations away from zero, this does not give any convincing evidence of CPT-violation.^[2]

Structure and geometry of charge distribution within the neutron

An article published in 2007 featuring a model-independent analysis concluded that the neutron has a negatively charged exterior, a positively charged middle, and a negative core.^[12] In a simplified classical view, the negative "skin" of the neutron assists it to be attracted to the protons with which it interacts in the nucleus. However, the main attraction between neutrons and protons is via the nuclear force, which does not involve charge.

Neutron compounds

Dineutrons and tetra-neutrons

The existence of stable clusters of 4 neutrons, or tetra-neutrons, has been hypothesised by a team led by Francisco-Miguel Marqués at the CNRS Laboratory for Nuclear Physics based on observations of the disintegration of beryllium-14 nuclei. This is particularly interesting because current theory suggests that these clusters should not be stable.

The dineutron is another hypothetical particle.

Neutronium and neutron stars

At extremely high pressures and temperatures, nucleons and electrons are believed to collapse into bulk neutronic matter, called neutronium. This is presumed to happen in neutron stars.

Detection

The common means of detecting a charged particle by looking for a track of ionization (such as in a cloud chamber) does not work for neutrons directly. Neutrons that elastically scatter off atoms can create an ionization track that is detectable, but the experiments are not as simple to carry out; other means for detecting neutrons, consisting of allowing them to interact with atomic nuclei, are more commonly used. The commonly used methods to detect neutrons can therefore be categorized according to the nuclear processes relied upon, mainly neutron capture or elastic scattering. A good discussion on neutron detection is found in chapter 14 of the book *Radiation Detection and Measurement* by Glenn F. Knoll (John Wiley & Sons, 1979).

Neutron detection by neutron capture

A common method for detecting neutrons involves converting the energy released from such reactions into electrical signals. Certain nuclides have neutron deficit and therefore a high probability to absorb a neutron. Upon neutron capture, the compound nucleus emits more easily detectable radiation, for example an alpha particle, which is then detected. The nuclides ^3He , ^6Li , ^{10}B , ^{233}U , ^{235}U , ^{237}Np and ^{239}Pu are useful for this purpose. These nuclides are rarely found in nature, but can be accumulated through processes such as isotopic enrichment.

The cross section for the process of neutron capture is much lower at high energies than at low energies. Therefore, the detection of neutrons by neutron capture requires a preceding slowing down of neutrons. For this purpose, a so-called moderator is used, typically a thick slab of polyethylene. Neutron detection according to the moderate-and-capture approach is not capable of measuring neutron energy, precise time of arrival, or direction of incidence, since this information is lost during moderation.

Neutron detection by elastic scattering

Neutrons can elastically scatter off nuclei, causing the struck nucleus to recoil. Kinematically, a neutron can transfer more energy to light nuclei such as hydrogen or helium than to heavier nuclei. Detectors relying on elastic scattering are called fast neutron detectors. Recoiling nuclei can ionize and excite further atoms through collisions. Charge and/or scintillation light produced in this way can be collected to produce a detected signal. A major challenge in fast neutron detection is discerning such signals from erroneous signals produced by gamma radiation in the same detector.

Fast neutron detectors have the advantage of not requiring a moderator, and therefore being capable of measuring the neutron's energy, time of arrival, and in certain cases direction of incidence.

Uses

The neutron plays an important role in many nuclear reactions. For example, neutron capture often results in neutron activation, inducing radioactivity. In particular, knowledge of neutrons and their behavior has been important in the development of nuclear reactors and nuclear weapons. The fissioning of elements like uranium-235 and plutonium-239 is caused by their absorption of neutrons.

Cold, thermal and hot neutron radiation is commonly employed in neutron scattering facilities, where the radiation is used in a similar way one uses X-rays for the analysis of condensed matter. Neutrons are complementary to the latter in terms of atomic contrasts by different scattering cross sections; sensitivity to magnetism; energy range for inelastic neutron spectroscopy; and deep penetration into matter.

The development of "neutron lenses" based on total internal reflection within hollow glass capillary tubes or by reflection from dimpled aluminum plates has driven ongoing research into neutron microscopy and neutron/gamma ray tomography.^{[13] [14] [15]}

A major use of neutrons is to excite delayed and prompt gamma rays from elements in materials. This forms the basis of neutron activation analysis (NAA) and prompt gamma neutron activation analysis (PGNAA). NAA is most often used to analyze small samples of materials in a nuclear reactor whilst PGNAA is most often used to analyze subterranean rocks around bore holes and industrial bulk materials on conveyor belts.

Another use of neutron emitters is the detection of light nuclei, particularly the hydrogen found in water molecules. When a fast neutron collides with a light nucleus, it loses a large fraction of its energy. By measuring the rate at which slow neutrons return to the probe after reflecting off of hydrogen nuclei, a neutron probe may determine the water content in soil.

Sources

Because free neutrons are unstable, they can be obtained only from nuclear disintegrations, nuclear reactions, and high-energy reactions (such as in cosmic radiation showers or accelerator collisions). Free neutron beams are obtained from neutron sources by neutron transport. For access to intense neutron sources, researchers must go to specialist facilities, such as the ISIS facility in the United Kingdom, which is currently the world's most intense pulsed neutron and muon source.

The neutron's lack of total electric charge makes it difficult to steer or accelerate them. Charged particles can be accelerated, decelerated, or deflected by electric or magnetic fields. These methods have little effect on neutrons beyond a small effect of an inhomogeneous magnetic field because of the neutron's magnetic moment. Neutrons can be controlled by methods that include moderation, reflection and velocity selection.

Protection

Exposure to free neutrons can be hazardous, since the interaction of neutrons with molecules in the body can cause disruption to molecules and atoms, and can also cause reactions which give rise to other forms of radiation (such as protons). The normal precautions of radiation protection apply: avoid exposure, stay as far from the source as possible, and keep exposure time to a minimum. Some particular thought must be given to how to protect from neutron exposure, however. For other types of radiation, e.g. alpha particles, beta particles, or gamma rays, material of a high atomic number and with high density make for good shielding; frequently lead is used. However, this approach will not work with neutrons, since the absorption of neutrons does not increase straightforwardly with atomic number, as it does with alpha, beta, and gamma radiation. Instead one needs to look at the particular interactions neutrons have with matter (see the section on detection above). For example, hydrogen rich materials are often used to shield against neutrons, since ordinary hydrogen both scatters and slows neutrons. This often means that simple concrete blocks or even paraffin-loaded plastic blocks afford better protection from neutrons than do far more dense materials. After slowing, neutrons may then be absorbed with an isotope which has high affinity for slow neutrons without causing secondary capture-radiation, such as lithium-6.

Hydrogen-rich ordinary water affects neutron absorption in nuclear fission reactors: usually neutrons are so strongly absorbed by normal water that fuel-enrichment with fissionable isotope is required. The deuterium in heavy water has a very much lower absorption affinity for neutrons than does protium (normal light hydrogen). Deuterium is therefore used in CANDU-type reactors, in order to slow (moderate) neutron velocity, to increase the probability of nuclear fission compared to neutron capture.

Production

Various nuclides become more stable by expelling neutrons as a decay mode; this is known as neutron emission, and happens commonly during spontaneous fission.

Cosmic radiation interacting with the Earth's atmosphere continuously generates neutrons that can be detected at the surface. Even stronger neutron radiation is produced at the surface of Mars where the atmosphere is thick enough to generate neutrons from cosmic ray spallation, but not thick enough to provide significant protection from the neutrons produced. These neutrons not only produce a Martian surface neutron radiation hazard from direct downward-going neutron radiation, but also a significant hazard from reflection of neutrons from the Martian surface, which will produce reflected neutron radiation penetrating upward into a Martian craft or habitat from the floor.^[16]



Institut Laue-Langevin (ILL) in Grenoble, France — one of the most important neutron research facilities worldwide

Nuclear fission reactors naturally produce free neutrons; their role is to sustain the energy-producing chain reaction. The intense neutron radiation can also be used to produce various radioisotopes through the process of neutron activation, which is a type of neutron capture.

Experimental nuclear fusion reactors produce free neutrons as a waste product. However, it is these neutrons that possess most of the energy, and converting that energy to a useful form has proved a difficult engineering challenge. Fusion reactors which generate neutrons are likely to create around twice the amount of radioactive waste of a fission reactor, but the waste is composed of neutron-activated lighter isotopes, which have relatively short (50–100 years) decay periods as compared to typical half lives of 10,000 years for fission waste, which is long primarily due to the long half life of alpha-emitting transuranic actinides.^[17] Nuclear power#Solid waste

Neutron temperature

Thermal neutrons

A **thermal neutron** is a free neutron that is Boltzmann distributed with $kT = 0.0253$ eV (4.0×10^{-21} J) at room temperature. This gives characteristic (not average, or median) speed of 2.2 km/s. The name 'thermal' comes from their energy being that of the room temperature gas or material they are permeating. (see *kinetic theory* for energies and speeds of molecules). After a number of collisions (often in the range of 10–20) with nuclei, neutrons arrive at this energy level, provided that they are not absorbed.

In many substances, thermal neutrons have a much larger effective cross-section than faster neutrons, and can therefore be absorbed more easily by any atomic nuclei that they collide with, creating a heavier — and often unstable — isotope of the chemical element as a result.

Most fission reactors use a neutron moderator to slow down, or *thermalize* the neutrons that are emitted by nuclear fission so that they are more easily captured, causing further fission. Others, called fast breeder reactors, use fission energy neutrons directly.

Cold neutrons

These neutrons are thermal neutrons that have been equilibrated in a very cold substance such as liquid deuterium. These are produced in neutron scattering research facilities.

Ultracold neutrons

Ultracold neutrons are produced by inelastically scattering cold neutrons in substances with a temperature of a few kelvins, such as solid deuterium or superfluid helium. An alternative production method is the mechanical deceleration of cold neutrons.

Fission energy neutrons

A **fast neutron** is a free neutron with a kinetic energy level close to 2 MeV (20 TJ/kg), hence a speed of 28,000 km/s. They are named *fission energy* or *fast* neutrons to distinguish them from lower-energy thermal neutrons, and high-energy neutrons produced in cosmic showers or accelerators. Fast neutrons are produced by nuclear processes such as nuclear fission.

Fast neutrons can be made into thermal neutrons via a process called moderation. This is done with a neutron moderator. In reactors, typically heavy water, light water, or graphite are used to moderate neutrons.

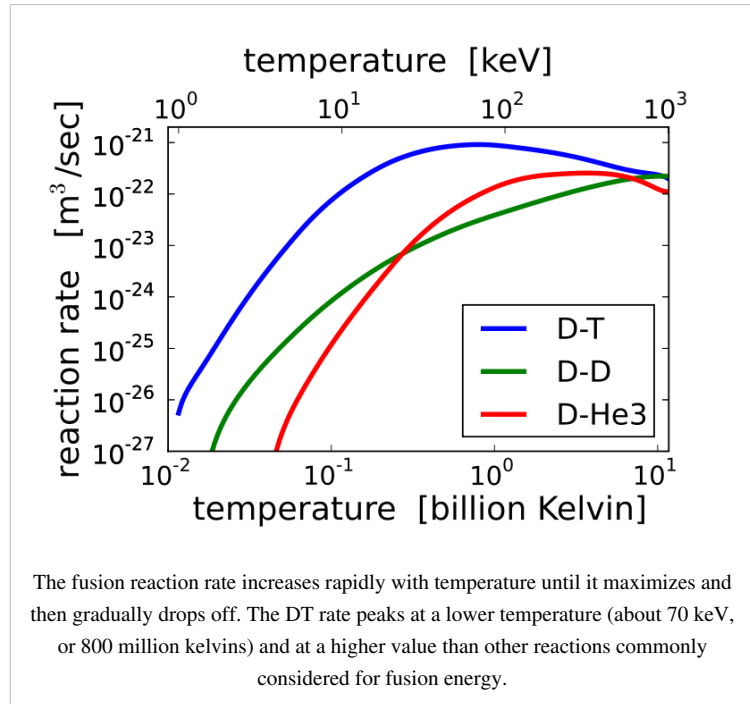
Fusion neutrons

D-T (deuterium-tritium) fusion is the fusion reaction that produces the most energetic neutrons, with 14.1 MeV of kinetic energy and traveling at 17% of the speed of light. D-T fusion is also the easiest fusion reaction to ignite, reaching near-peak rates even when the deuterium and tritium nuclei have only a thousandth as much kinetic energy as the 14.1 MeV that will be produced.

14.1 MeV neutrons have about 10 times as much energy as fission neutrons, and are very effective at fissioning even non-fissile heavy nuclei, and these high-energy fissions produce more neutrons on average than fissions by lower-energy neutrons. This makes D-T fusion neutron sources such as proposed tokamak power reactors useful for transmutation of transuranic waste. 14.1 MeV neutrons can also produce neutrons by knocking them loose from nuclei.

On the other hand, these very high energy neutrons are less likely to simply be captured without causing fission or spallation. For these reasons, nuclear weapon design extensively utilizes D-T fusion 14.1 MeV neutrons to cause more fission. Fusion neutrons are able to cause fission in ordinarily non-fissile materials, such as depleted uranium (uranium-238), and these materials have been used in the jackets of thermonuclear weapons. Fusion neutrons also can cause fission in substances that are unsuitable or difficult to make into primary fission bombs, such as reactor grade plutonium. This physical fact thus causes ordinary non-weapons grade materials to become of concern in certain nuclear proliferation discussions and treaties.

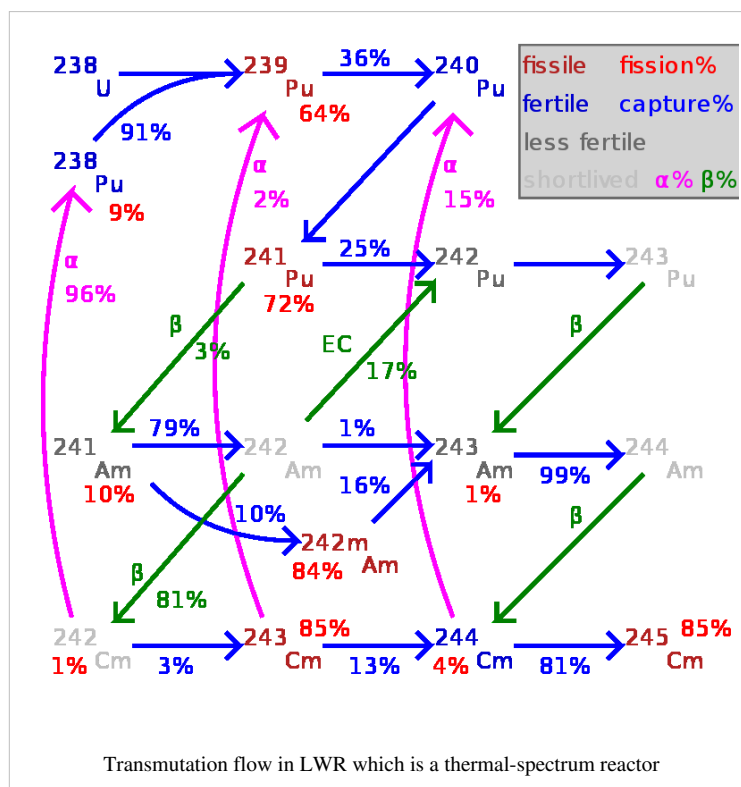
Other fusion reactions produce much less energetic neutrons. D-D fusion produces a 2.45 MeV neutron and helium-3 half of the time, and produces tritium and a proton but no neutron the other half of the time. D-³He fusion produces no neutron.



Intermediate-energy neutrons

A fission energy neutron that has slowed down but not yet reached thermal energies is called an epithermal neutron.

Cross sections for both capture and fission reactions often have multiple resonance peaks at specific energies in the epithermal energy range. These are of less significance in a fast neutron reactor where most neutrons are absorbed before slowing down to this range, or in a well-moderated thermal reactor where epithermal neutrons mostly interact with moderator nuclei, not with either fissile or fertile actinide nuclides. However, in a partially moderated reactor with more interactions of epithermal neutrons with heavy metal nuclei, there are greater possibilities for transient changes in reactivity which might make reactor control more difficult.



Ratios of capture reactions to fission reactions are also worse (more captures without fission) in most nuclear fuels such as plutonium-239, making epithermal-spectrum reactors using these fuels less desirable, as captures not only waste the one neutron captured but also usually result in a nuclide which is not fissile with thermal or epithermal neutrons, though still fissionable with fast neutrons. The exception is uranium-233 of the thorium cycle which has good capture-fission ratios at all neutron energies.

High-energy neutrons

These neutrons have more energy than fission energy neutrons and are generated as secondary particles by particle accelerators or in the atmosphere from cosmic rays. They can have energies as high as tens of joules per neutron.

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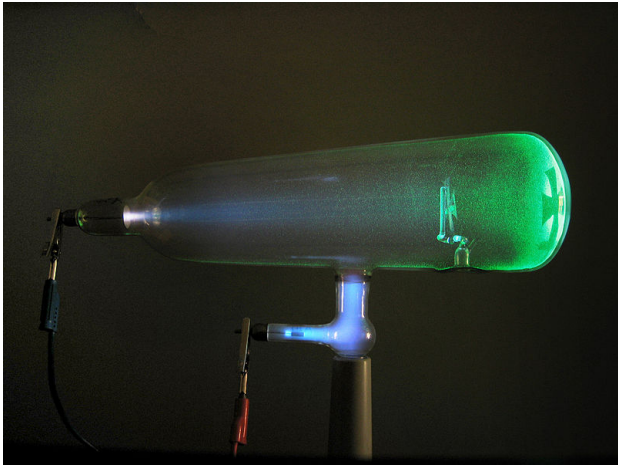
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Electron

Electron	
	
Experiments with a Crookes tube first demonstrated the particle nature of electrons. In this illustration, the profile of the cross-shaped target is projected against the tube face at right by a beam of electrons. ^[1]	
Composition:	Elementary particle ^[2]
Particle statistics:	Fermionic
Group:	Lepton
Generation:	First
Interaction:	Gravity, Electromagnetic, Weak
Symbol(s):	e^- , β^-
Antiparticle:	Positron (also called antielectron)
Theorized:	Richard Laming (1838–1851), ^[3] G. Johnstone Stoney (1874) and others. ^{[4] [5]}
Discovered:	J. J. Thomson (1897) ^[6]
Mass:	$9.10938215(45) \times 10^{-31} \text{ kg}$ ^[7] $5.4857990943(23) \times 10^{-4} \text{ u}$ ^[7] $[1822.88850204(77)]^{-1} \text{ u}$ ^[8] $0.510998910(13) \text{ MeV}/c^2$ ^[7]
Electric charge:	-1 e ^[9] $-1.602176487(40) \times 10^{-19} \text{ C}$ ^[7] $-4.803 \times 10^{-10} \text{ esu}$ ^[10]
Magnetic moment:	$-1.00115965218111 \mu_B$ ^[7]
Spin:	$\frac{1}{2}$

The **electron** is a subatomic particle carrying a negative electric charge. It has no known components or substructure. Therefore, the electron is generally believed to be an elementary particle.^[2] An electron has a mass that is approximately 1/1836 that of the proton.^[11] The intrinsic angular momentum (spin) of the electron is a half-integer value in units of $\hbar$, which means that it is a fermion. The antiparticle of the electron is called the positron. The positron is identical to the electron except that it carries electrical and other charges of the opposite sign. When an electron collides with a positron, both particles may either scatter off each other or be totally annihilated, producing a

pair (or more) of gamma ray photons. Electrons, which belong to the first generation of the lepton particle family,^[12] participate in gravitational, electromagnetic and weak interactions.^[13] Electrons, like all matter, have quantum mechanical properties of both particles and waves, so they can collide with other particles and be diffracted like light. However, this duality is best demonstrated in experiments with electrons, due to their tiny mass. Since an electron is a fermion, no two electrons can occupy the same quantum state, in accordance with the Pauli exclusion principle.^[12]

The concept of an indivisible amount of electric charge was theorized to explain the chemical properties of atoms, beginning in 1838 by British natural philosopher Richard Laming;^[4] the name *electron* was introduced for this charge in 1894 by Irish physicist George Johnstone Stoney. The electron was identified as a particle in 1897 by J. J. Thomson and his team of British physicists.^{[6] [14] [15]}

In many physical phenomena, such as electricity, magnetism, and thermal conductivity, electrons play an essential role. An electron in motion relative to an observer generates a magnetic field, and will be deflected by external magnetic fields. When an electron is accelerated, it can absorb or radiate energy in the form of photons. Electrons, together with atomic nuclei made of protons and neutrons, make up atoms. However, electrons contribute less than 0.06% to an atom's total mass. The attractive Coulomb force between an electron and a proton causes electrons to be bound into atoms. The exchange or sharing of the electrons between two or more atoms is the main cause of chemical bonding.^[16]

According to theory, most electrons in the universe were created in the big bang, but they may also be created through beta decay of radioactive isotopes and in high-energy collisions, for instance when cosmic rays enter the atmosphere. Electrons may be destroyed through annihilation with positrons, and may be absorbed during nucleosynthesis in stars. Laboratory instruments are capable of containing and observing individual electrons as well as electron plasma, whereas dedicated telescopes can detect electron plasma in outer space. Electrons have many applications, including welding, cathode ray tubes, electron microscopes, radiation therapy, lasers and particle accelerators.

History

The ancient Greeks noticed that amber attracted small objects when rubbed with fur. Apart from lightning, this phenomenon is humanity's earliest recorded experience with electricity.^[17] In his 1600 treatise *De Magnete*, the English scientist William Gilbert coined the New Latin term *electricus*, to refer to this property of attracting small objects after being rubbed.^[18] Both *electric* and *electricity* are derived from the Latin *ēlectrum* (also the root of the alloy of the same name), which came from the Greek word ἤλεκτρον (*ēlektron*) for amber.

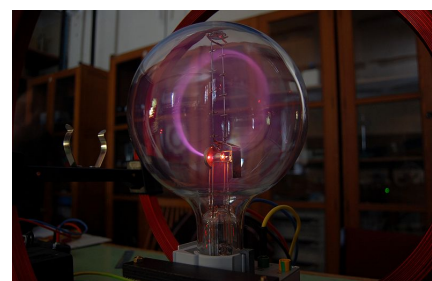
In 1737 C. F. du Fay and Hawksbee independently discovered what they believed to be two kinds of frictional electricity; one generated from rubbing glass, the other from rubbing resin. From this, Du Fay theorized that electricity consists of two electrical fluids, "vitreous" and "resinous", that are separated by friction and that neutralize each other when combined.^[19] A decade later Benjamin Franklin proposed that electricity was not from different types of electrical fluid, but the same electrical fluid under different pressures. He gave them the modern charge nomenclature of positive and negative respectively.^[20] Franklin thought that the charge carrier was positive.^[21]

Between 1838 and 1851, British natural philosopher Richard Laming developed the idea that an atom is composed of a core of matter surrounded by subatomic particles that had unit electric charges.^[3] Beginning in 1846, German physicist William Weber theorized that electricity was composed of positively and negatively charged fluids, and their interaction was governed by the inverse square law. After studying the phenomenon of electrolysis in 1874, Irish physicist George Johnstone Stoney suggested that there existed a "single definite quantity of electricity", the charge of a monovalent ion. He was able to estimate the value of this elementary charge *e* by means of Faraday's laws of electrolysis.^[22] However, Stoney believed these charges were permanently attached to atoms and could not be removed. In 1881, German physicist Hermann von Helmholtz argued that both positive and negative charges were divided into elementary parts, each of which "behaves like atoms of electricity".^[4]

In 1894, Stoney coined the term *electron* to describe these elementary charges, saying, "... an estimate was made of the actual amount of this most remarkable fundamental unit of electricity, for which I have since ventured to suggest the name *electron*".^[23] The word *electron* is a combination of the word *electric* and the suffix *-on*, with the latter now used to designate a subatomic particle, such as a proton or neutron.^{[24] [25]}

Discovery

The German physicist Johann Wilhelm Hittorf undertook the study of electrical conductivity in rarefied gases. In 1869, he discovered a glow emitted from the cathode that increased in size with decrease in gas pressure. In 1876, the German physicist Eugen Goldstein showed that the rays from this glow cast a shadow, and he dubbed the rays cathode rays.^[27] During the 1870s, the English chemist and physicist Sir William Crookes developed the first cathode ray tube to have a high vacuum inside.^[28] He then showed that the luminescence rays appearing within the tube carried energy and moved from the cathode to the anode. Furthermore, by applying a magnetic field, he was able to deflect the rays, thereby demonstrating that the beam behaved as though it were negatively charged.^{[29] [30]} In 1879, he proposed that these properties could be explained by what he termed 'radiant matter'. He suggested that this was a fourth state of matter, consisting of negatively charged molecules that were being projected with high velocity from the cathode.^[31]



A beam of electrons deflected in a circle by a magnetic field^[26]

The German-born British physicist Arthur Schuster expanded upon Crookes' experiments by placing metal plates in parallel to the cathode rays and applying an electric potential between the plates. The field deflected the rays toward the positively charged plate, providing further evidence that the rays carried negative charge. By measuring the amount of deflection for a given level of current, in 1890 Schuster was able to estimate the charge-to-mass ratio of the ray components. However, this produced a value that was more than a thousand times greater than what was expected, so little credence was given to his calculations at the time.^{[29] [32]}

In 1896, the British physicist J. J. Thomson, with his colleagues John S. Townsend and H. A. Wilson,^[14] performed experiments indicating that cathode rays really were unique particles, rather than waves, atoms or molecules as was believed earlier.^[6] Thomson made good estimates of both the charge e and the mass m , finding that cathode ray particles, which he called "corpuscles," had perhaps one thousandth of the mass of the least massive ion known: hydrogen.^{[6] [15]} He showed that their charge to mass ratio, e/m , was independent of cathode material. He further showed that the negatively charged particles produced by radioactive materials, by heated materials and by illuminated materials were universal.^{[6] [33]} The name electron was again proposed for these particles by the Irish physicist George F. Fitzgerald, and the name has since gained universal acceptance.^[29]

While studying naturally fluorescing minerals in 1896, the French physicist Henri Becquerel discovered that they emitted radiation without any exposure to an external energy source. These radioactive materials became the subject of much interest by scientists, including the New Zealand physicist Ernest Rutherford who discovered they emitted particles. He designated these particles alpha and beta, on the basis of their ability to penetrate matter.^[34] In 1900, Becquerel showed that the beta rays emitted by radium could be deflected by an electric field, and that their mass-to-charge ratio was the same as for cathode rays.^[35] This evidence strengthened the view that electrons existed as components of atoms.^{[36] [37]}

The electron's charge was more carefully measured by the American physicist Robert Millikan in his oil-drop experiment of 1909, the results of which he published in 1911. This experiment used an electric field to prevent a charged droplet of oil from falling as a result of gravity. This device could measure the electric charge from as few as 1–150 ions with an error margin of less than 0.3%. Comparable experiments had been done earlier by Thomson's team,^[6] using clouds of charged water droplets generated by electrolysis,^[14] and in 1911 by Abram Ioffe, who

independently obtained the same result as Millikan using charged microparticles of metals, then published his results in 1913.^[38] However, oil drops were more stable than water drops because of their slower evaporation rate, and thus more suited to precise experimentation over longer periods of time.^[39]

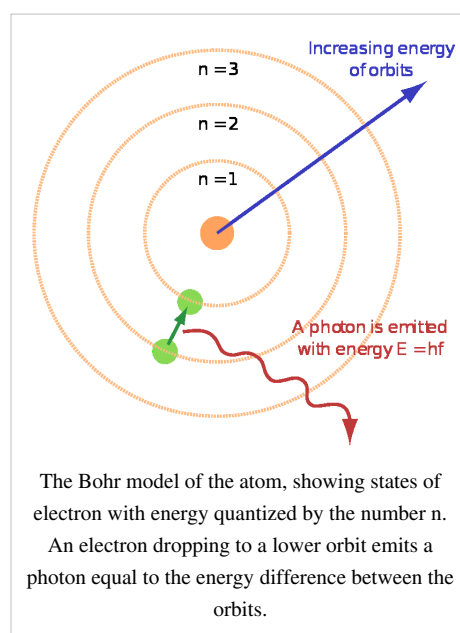
Around the beginning of the twentieth century, it was found that under certain conditions a fast moving charged particle caused a condensation of supersaturated water vapor along its path. In 1911, Charles Wilson used this principle to devise his cloud chamber, allowing the tracks of charged particles, such as fast-moving electrons, to be photographed.^[40]

Atomic theory

By 1914, experiments by physicists Ernest Rutherford, Henry Moseley, James Franck and Gustav Hertz had largely established the structure of an atom as a dense nucleus of positive charge surrounded by lower-mass electrons.^[41] In 1913, Danish physicist Niels Bohr postulated that electrons resided in quantized energy states, with the energy determined by the angular momentum of the electron's orbits about the nucleus. The electrons could move between these states, or orbits, by the emission or absorption of photons at specific frequencies. By means of these quantized orbits, he accurately explained the spectral lines of the hydrogen atom.^[42] However, Bohr's model failed to account for the relative intensities of the spectral lines and it was unsuccessful in explaining the spectra of more complex atoms.^[41]

Chemical bonds between atoms were explained by Gilbert Newton Lewis, who in 1916 proposed that a covalent bond between two atoms is maintained by a pair of electrons shared between them.^[43] Later, in 1923, Walter Heitler and Fritz London gave the full explanation of the electron-pair formation and chemical bonding in terms of quantum mechanics.^[44] In 1919, the American chemist Irving Langmuir elaborated on the Lewis' static model of the atom and suggested that all electrons were distributed in successive "concentric (nearly) spherical shells, all of equal thickness".^[45] The shells were, in turn, divided by him in a number of cells each containing one pair of electrons. With this model Langmuir was able to qualitatively explain the chemical properties of all elements in the periodic table,^[44] which were known to largely repeat themselves according to the periodic law.^[46]

In 1924, Austrian physicist Wolfgang Pauli observed that the shell-like structure of the atom could be explained by a set of four parameters that defined every quantum energy state, as long as each state was inhabited by no more than a single electron. (This prohibition against more than one electron occupying the same quantum energy state became known as the Pauli exclusion principle.)^[47] The physical mechanism to explain the fourth parameter, which had two distinct possible values, was provided by the Dutch physicists Abraham Goudsmith and George Uhlenbeck when they suggested that an electron, in addition to the angular momentum of its orbit, could possess an intrinsic angular momentum.^[41] ^[48] This property became known as spin, and explained the previously mysterious splitting of spectral lines observed with a high-resolution spectrograph; this phenomenon is known as fine structure splitting.^[49]



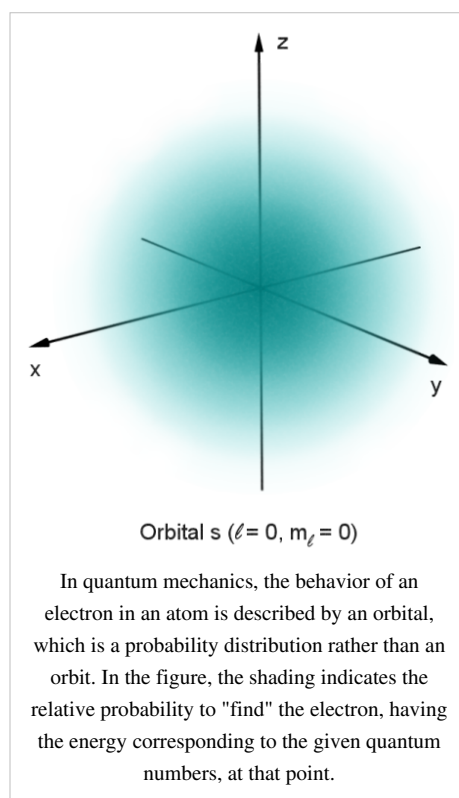
Quantum mechanics

In his 1924 dissertation *Recherches sur la théorie des quanta* (Research on Quantum Theory), French physicist Louis de Broglie hypothesized that all matter possesses a De Broglie wave similar to light.^[50] That is, under the appropriate conditions, electrons and other matter would show properties of either particles or waves. The corpuscular properties of a particle are demonstrated when it is shown to have a localized position in space along its trajectory at any given moment.^[51] Wave-like nature is observed, for example, when a beam of light is passed through parallel slits and creates interference patterns. In 1927, the interference effect was demonstrated with a beam of electrons by English physicist George Paget Thomson with a thin metal film and by American physicists Clinton Davisson and Lester Germer using a crystal of nickel.^[52]

The success of de Broglie's prediction led to the publication, by Erwin Schrödinger in 1926, of the Schrödinger equation that successfully describes how electron waves propagated.^[53] Rather than yielding a solution that determines the location of an electron over time, this wave equation can be used to predict the probability of finding an electron near a position. This approach was later called quantum mechanics, which provided an extremely close derivation to the energy states of an electron in a hydrogen atom.^[54] Once spin and the interaction between multiple electrons were considered, quantum mechanics allowed the configuration of electrons in atoms with higher atomic numbers than hydrogen to be successfully predicted.^[55]

In 1928, building on Wolfgang Pauli's work, Paul Dirac produced a model of the electron - the Dirac equation, consistent with relativity theory, by applying relativistic and symmetry considerations to the hamiltonian formulation of the quantum mechanics of the electro-magnetic field.^[56] In order to resolve some problems within his relativistic equation, in 1930 Dirac developed a model of the vacuum as an infinite sea of particles having negative energy, which was dubbed the Dirac sea. This led him to predict the existence of a positron, the antimatter counterpart of the electron.^[57] This particle was discovered in 1932 by Carl D. Anderson, who proposed calling standard electrons *negatrons*, and using *electron* as a generic term to describe both the positively and negatively charged variants. This usage of the term 'negatron' is still occasionally encountered today, and it may be shortened to 'negaton'.^[58] ^[59]

In 1947 Willis Lamb, working in collaboration with graduate student Robert Rutherford, found that certain quantum states of hydrogen atom, which should have the same energy, were shifted in relation to each other, the difference being the Lamb shift. About the same time, Polykarp Kusch, working with Henry M. Foley, discovered the magnetic moment of the electron is slightly larger than predicted by Dirac's theory. This small difference was later called anomalous magnetic dipole moment of the electron. To resolve these issues, a refined theory called quantum electrodynamics was developed by Sin-Itiro Tomonaga, Julian Schwinger and Richard P. Feynman in the late 1940s.^[60]



Particle accelerators

With the development of the particle accelerator during the first half of the twentieth century, physicists began to delve deeper into the properties of subatomic particles.^[61] The first successful attempt to accelerate electrons using Electromagnetic induction was made in 1942 by Donald Kerst. His initial betatron reached energies of 2.3 MeV, while subsequent betatrons achieved 300 MeV. In 1947, synchrotron radiation was discovered with a 70 MeV electron synchrotron at General Electric. This radiation was caused by the acceleration of electrons, moving near the speed of light, through a magnetic field.^[62]

With a beam energy of 1.5 GeV, the first high-energy particle collider was ADONE, which began operations in 1968.^[63] This device accelerated electrons and positrons in opposite directions, effectively doubling the energy of their collision when compared to striking a static target with an electron.^[64] The Large Electron-Positron Collider (LEP) at CERN, which was operational from 1989 to 2000, achieved collision energies of 209 GeV and made important measurements for the Standard Model of particle physics.^{[65] [66]}

Characteristics

Classification

In the Standard Model of particle physics, electrons belong to the group of subatomic particles called leptons, which are believed to be fundamental or elementary particles. Electrons have the lowest mass of any charged lepton (or electrically charged particle of any type) and belong to the first-generation of fundamental particles.^[67] The second and third generation contain charged leptons, the muon and the tau, which are identical to the electron in charge, spin and interactions, but are more massive. Leptons differ from the other basic constituent of matter, the quarks, by their lack of strong interaction. All members of the lepton group are fermions, because they all have half-odd integer spin; the electron has spin $\frac{1}{2}$.^[68]

Fundamental properties

The invariant mass of an electron is approximately 9.109×10^{-31} kilogram,^[7] or 5.489×10^{-4} atomic mass unit. On the basis of Einstein's principle of mass–energy equivalence, this mass corresponds to a rest energy of 0.511 MeV. The ratio between the mass of a proton and that of an electron is about 1836.^{[11] [69]} Astronomical measurements show that the proton-to-electron mass ratio has held the same value for at least half the age of the universe, as is predicted by the Standard Model.^[70]

Electrons have an electric charge of -1.602×10^{-19} coulomb,^[7] which is used as a standard unit of charge for subatomic particles. Within the limits of experimental accuracy, the electron charge is identical to the charge of a proton, but with the opposite sign.^[71] As the symbol e is used for the elementary charge, the electron is commonly symbolized by e^- , where the minus sign indicates the negative charge. The positron is symbolized by e^+ because it

Three Generations of Matter (Fermions)				
	I	II	III	
mass→	2.4 MeV	1.27 GeV	171.2 GeV	0
charge→	$\frac{2}{3}$	$\frac{2}{3}$	$\frac{2}{3}$	0
spin→	$\frac{1}{2}$	$\frac{1}{2}$	$\frac{1}{2}$	1
name→	u up	c charm	t top	γ photon
Quarks	4.8 MeV $-\frac{1}{3}$ $\frac{1}{2}$ d down	104 MeV $-\frac{1}{3}$ $\frac{1}{2}$ s strange	4.2 GeV $-\frac{1}{3}$ $\frac{1}{2}$ b bottom	0 0 1 g gluon
	<2.2 eV 0 $\frac{1}{2}$ ν_e electron neutrino	<0.17 MeV 0 $\frac{1}{2}$ ν_μ muon neutrino	<15.5 MeV 0 $\frac{1}{2}$ ν_τ tau neutrino	91.2 GeV 0 0 1 Z ⁰ weak force
	0.511 MeV -1 $\frac{1}{2}$ e electron	105.7 MeV -1 $\frac{1}{2}$ μ muon	1.777 GeV -1 $\frac{1}{2}$ τ tau	80.4 GeV ± 1 1 W ^{$\pm$} weak force
Leptons				Bosons (Forces)

Standard Model of elementary particles. The electron is at lower left.

has the same properties as the electron but with a positive rather than negative charge.^{[7] [68]}

The electron has an intrinsic angular momentum or spin of $\frac{1}{2}$.^[7] This property is usually stated by referring to the electron as a spin- $\frac{1}{2}$ particle.^[68] For such particles the spin magnitude is $\sqrt{3}/2 \hbar$.^[72] while the result of the measurement of a projection of the spin on any axis can only be $\pm \hbar/2$. In addition to spin, the electron has an intrinsic magnetic moment along its spin axis.^[7] It is approximately equal to one Bohr magneton,^{[73] [74]} which is a physical constant equal to $9.27400915(23) \times 10^{-24}$ joules per tesla.^[7] The orientation of the spin with respect to the momentum of the electron defines the property of elementary particles known as helicity.^[75]

The electron has no known substructure.^{[2] [76]} Hence, it is defined or assumed to be a point particle with a point charge and no spatial extent.^[12] Observation of a single electron in a Penning trap shows the upper limit of the particle's radius is 10^{-22} meters.^[77] There is a physical constant called the "classical electron radius", with the much larger value of 2.8179×10^{-15} m. However, the terminology comes from a simplistic calculation that ignores the effects of quantum mechanics; in reality, the so-called classical electron radius has little to do with the true fundamental structure of the electron.^{[78] [79]}

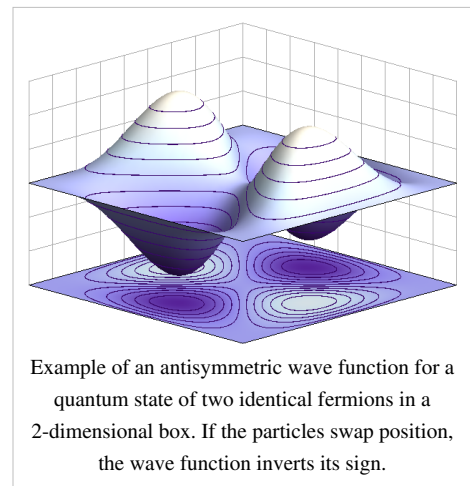
There are elementary particles that spontaneously decay into less massive particles. An example is the muon, which decays into an electron, a neutrino and an antineutrino, with a mean lifetime of 2.2×10^{-6} seconds. However, the electron is thought to be stable on theoretical grounds: the electron is the least massive particle with non-zero electric charge, so its decay would violate charge conservation.^[80] The experimental lower bound for the electron's mean lifetime is 4.6×10^{26} years, at a 90% confidence level.^[81]

Quantum properties

As with all particles, electrons can act as waves. This is called the wave–particle duality and can be demonstrated using the double-slit experiment. The wave-like nature of the electron allows it to pass through two parallel slits simultaneously, rather than just one slit as would be the case for a classical particle. In quantum mechanics, the wave-like property of one particle can be described mathematically as a complex-valued function, the wave function, commonly denoted by the Greek letter psi (ψ). When the absolute value of this function is squared, it gives the probability that a particle will be observed near a location—a probability density.^[82]

Electrons are identical particles because they cannot be distinguished from each other by their intrinsic physical properties. In quantum mechanics, this means that a pair of interacting electrons must be able to swap positions without an observable change to the state of the system. The wave function of fermions, including electrons, is antisymmetric, meaning that it changes sign when two electrons are swapped; that is, $\psi(r_1, r_2) = -\psi(r_2, r_1)$, where the variables r_1 and r_2 correspond to the first and second electrons, respectively. Since the absolute value is not changed by a sign swap, this corresponds to equal probabilities. Bosons, such as the photon, have symmetric wave functions instead.^[82]

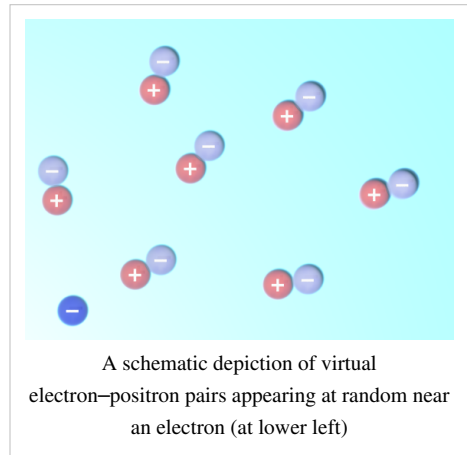
In the case of antisymmetry, solutions of the wave equation for interacting electrons result in a zero probability that each pair will occupy the same location or state. This is responsible for the Pauli exclusion principle, which precludes any two electrons from occupying the same quantum state. This principle explains many of the properties of electrons. For example, it causes groups of bound electrons to occupy different orbitals in an atom, rather than all overlapping each other in the same orbit.^[82]



Virtual particles

Physicists believe that empty space may be continually creating pairs of virtual particles, such as a positron and electron, which rapidly annihilate each other shortly thereafter.^[83] The combination of the energy variation needed to create these particles, and the time during which they exist, fall under the threshold of detectability expressed by the Heisenberg uncertainty relation, $\Delta E \cdot \Delta t \geq \hbar$. In effect, the energy needed to create these virtual particles, ΔE , can be "borrowed" from the vacuum for a period of time, Δt , so that their product is no more than the reduced Planck constant, $\hbar \approx 6.6 \times 10^{-16} \text{ eV}\cdot\text{s}$. Thus, for a virtual electron, Δt is at most $1.3 \times 10^{-21} \text{ s}$.^[84]

While an electron–positron virtual pair is in existence, the coulomb force from the ambient electric field surrounding an electron causes a created positron to be attracted to the original electron, while a created electron experiences a repulsion. This causes what is called vacuum polarization. In effect, the vacuum behaves like a medium having a dielectric permittivity more than unity. Thus the effective charge of an electron is actually smaller than its true value, and the charge decreases with increasing distance from the electron.^{[85] [86]} This polarization was confirmed experimentally in 1997 using the Japanese TRISTAN particle accelerator.^[87] Virtual particles cause a comparable shielding effect for the mass of the electron.^[88]



The interaction with virtual particles also explains the small (about 0.1%) deviation of the intrinsic magnetic moment of the electron from the Bohr magneton (the anomalous magnetic moment).^{[73] [89]} The extraordinarily precise agreement of this predicted difference with the experimentally determined value is viewed as one of the great achievements of quantum electrodynamics.^[90]

In classical physics, the angular momentum and magnetic moment of an object depend upon its physical dimensions. Hence, the concept of a dimensionless electron possessing these properties might seem inconsistent. The apparent paradox can be explained by the formation of virtual photons in the electric field generated by the electron. These photons cause the electron to shift about in a jittery fashion (known as *zitterbewegung*),^[91] which results in a net circular motion with precession. This motion produces both the spin and the magnetic moment of the electron.^{[12] [92]} In atoms, this creation of virtual photons explains the Lamb shift observed in spectral lines.^[85]

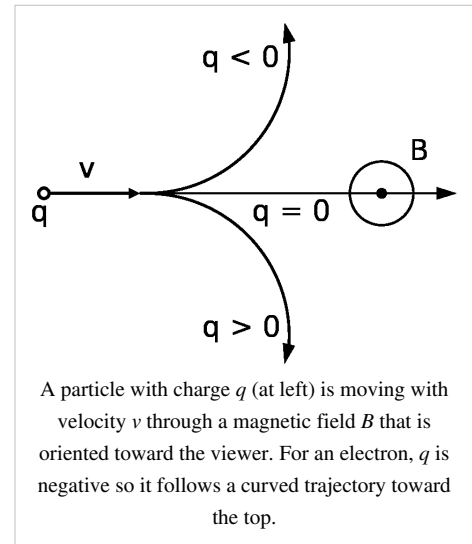
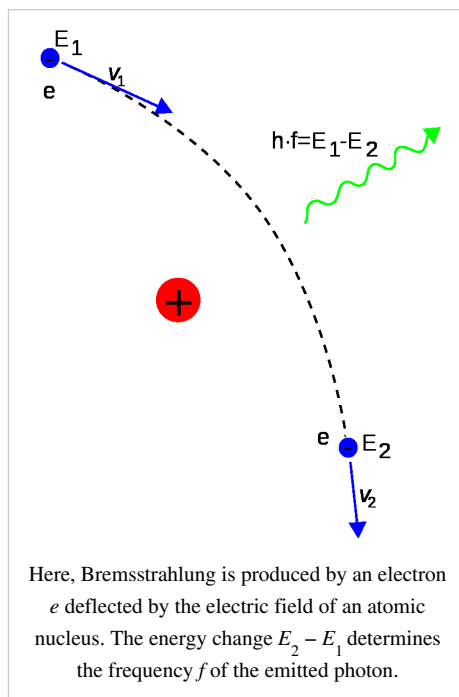
Interaction

An electron generates an electric field that exerts an attractive force on a particle with a positive charge, such as the proton, and a repulsive force on a particle with a negative charge. The strength of this force is determined by Coulomb's inverse square law.^[93] When an electron is in motion, it generates a magnetic field.^[94] The Ampère-Maxwell law relates the magnetic field to the mass motion of electrons (the current) with respect to an observer. It is this property of induction which supplies the magnetic field that drives an electric motor.^[95] The electromagnetic field of an arbitrary moving charged particle is expressed by the Liénard–Wiechert potentials, which are valid even when the particle's speed is close to that of light (relativistic).

When an electron is moving through a magnetic field, it is subject to the Lorentz force that exerts an influence in a direction perpendicular to the plane defined by the magnetic field and the electron velocity. This centripetal force causes the electron to follow a helical trajectory through the field at a radius called the gyroradius. The acceleration from this curving motion induces the electron to radiate energy in the form of synchrotron radiation.^{[96] [97] [98]} The energy emission in turn causes a recoil of the electron, known as the Abraham-Lorentz-Dirac force, which creates a friction that slows the electron. This force is caused by a back-reaction of the electron's own field upon itself.^[99]

In quantum electrodynamics the electromagnetic interaction between particles is mediated by photons. An isolated electron that is not undergoing acceleration is unable to emit or absorb a real photon; doing so would violate conservation of energy and momentum.

Instead, virtual photons can transfer momentum between two charged particles. It is this exchange of virtual photons that, for example, generates the Coulomb force.^[100] Energy emission can occur when a moving electron is deflected by a charged particle, such as a proton. The acceleration of the electron results in the emission of Bremsstrahlung radiation.^[101]



An inelastic collision between a photon (light) and a solitary (free) electron is called Compton scattering. This collision results in a transfer of momentum and energy between the particles, which modifies the wavelength of the photon by an amount called the Compton shift.^[102] The maximum magnitude of this wavelength shift is $h/m_e c$, which is known as the Compton wavelength.^[103] For an electron, it has a value of 2.43×10^{-12} m.^[7] When the wavelength of the light is long (for instance, the wavelength of the visible light is $0.4\text{--}0.7\text{ }\mu\text{m}$) the wavelength shift becomes negligible. Such interaction between the light and free electrons is called Thomson scattering or Linear Thomson scattering.^[104]

The relative strength of the electromagnetic interaction between two charged particles, such as an electron and a proton, is given by the fine-structure constant. This value is a dimensionless quantity formed by the ratio of two energies: the electrostatic energy of attraction (or repulsion) at a separation of one Compton wavelength, and the rest

energy of the charge. It is given by $\alpha \approx 7.297353 \times 10^{-3}$, which is approximately equal to $1/137$.^[7]

When electrons and positrons collide, they annihilate each other, giving rise to two or more gamma ray photons. If the electron and positron have negligible momentum, a positronium atom can form before annihilation results in two or three gamma ray photons totalling 1.022 MeV.^{[105] [106]} On the other hand, high-energy photons may transform into an electron and a positron by a process called pair production, but only in the presence of a nearby charged particle, such as a nucleus.^{[107] [108]}

In the theory of electroweak interaction, the left-handed component of electron's wavefunction forms a weak isospin doublet with the electron neutrino. This means that during weak interactions, electron neutrinos behave like electrons. Either member of this doublet can undergo a charged current interaction by emitting or absorbing a W and be converted into the other member. Charge is conserved during this reaction because the W boson also carries a charge, canceling out any net change during the transmutation. Charged current interactions are responsible for the phenomenon of beta decay in a radioactive atom. Both the electron and electron neutrino can undergo a neutral current interaction via a Z^0 exchange, and this is responsible for neutrino-electron elastic scattering.^[109]

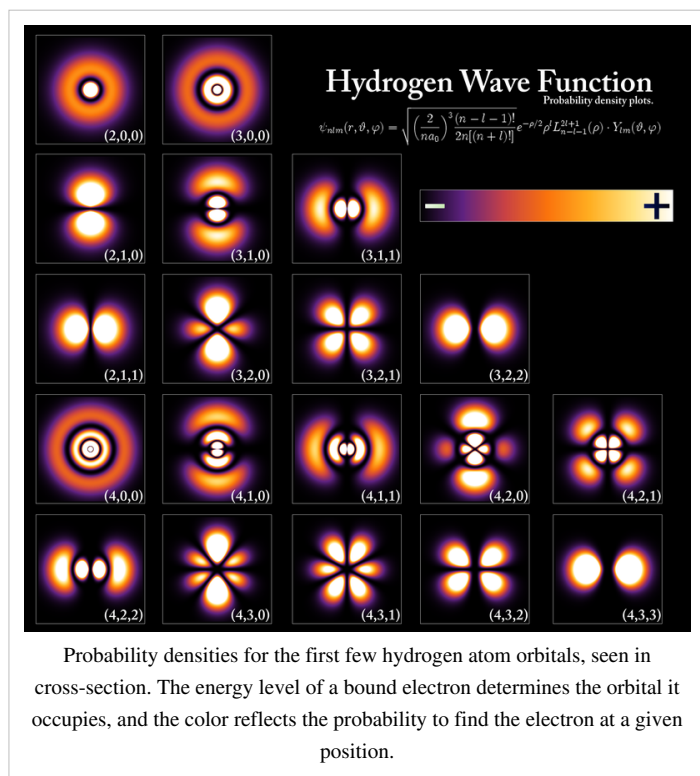
Atoms and molecules

An electron can be *bound* to the nucleus of an atom by the attractive Coulomb force. A system of several electrons bound to a nucleus is called an atom. If the number of electrons is different from the nucleus' electrical charge, such an atom is called an ion. The wave-like behavior of a bound electron is described by a function called an atomic orbital. Each orbital has its own set of quantum numbers such as energy, angular momentum and projection of angular momentum, and only a discrete set of these orbitals exist around the nucleus. According to the Pauli exclusion principal each orbital can be occupied by up to two electrons, which must differ in their spin quantum number.

Electrons can transfer between different orbitals by the emission or absorption of photons with an energy that matches the difference in potential.^[110] Other methods of orbital transfer include collisions with particles, such as electrons, and the Auger effect.^[111] In order to escape the atom, the energy of the electron must be increased above its binding energy to the atom. This occurs, for example, with the photoelectric effect, where an incident photon exceeding the atom's ionization energy is absorbed by the electron.^[112]

The orbital angular momentum of electrons is quantized. Because the electron is charged, it produces an orbital magnetic moment that is proportional to the angular momentum. The net magnetic moment of an atom is equal to the vector sum of orbital and spin magnetic moments of all electrons and the nucleus. The nuclear magnetic moment is, however, negligible in comparison to the effect from the electrons. The magnetic moments of the electrons that occupy the same orbital (so called, paired electrons) cancel each other out.^[113]

The chemical bond between atoms occurs as a result of electromagnetic interactions, as described by the laws of quantum mechanics.^[114] The strongest bonds are formed by the sharing or transfer of electrons between atoms,



allowing the formation of molecules.^[116] Within a molecule, electrons move under the influence of several nuclei, and occupy molecular orbitals; much as they can occupy atomic orbitals in isolated atoms.^[115] A fundamental factor in these molecular structures is the existence of electron pairs. These are electrons with opposed spins, allowing them to occupy the same molecular orbital without violating the Pauli exclusion principle (much like in atoms). Different molecular orbitals have different spatial distribution of the electron density. For instance, in bonded pairs (i.e. in the pairs that actually bind atoms together) electrons can be found with the maximal probability in a relatively small volume between the nuclei. On the contrary, in non-bonded pairs electrons are distributed in a large volume around nuclei.^[116]

Conductivity

If a body has more or fewer electrons than are required to balance the positive charge of the nuclei, then that object has a net electric charge. When there is an excess of electrons, the object is said to be negatively charged. When there are fewer electrons than the number of protons in nuclei, the object is said to be positively charged. When the number of electrons and the number of protons are equal, their charges cancel each other and the object is said to be electrically neutral. A macroscopic body can develop an electric charge through rubbing, by the triboelectric effect.^[120]

Independent electrons moving in vacuum are termed *free* electrons. Electrons in metals also behave as if they were free. In reality the particles that are commonly termed electrons in metals and other solids are quasi-electrons—quasi-particles, which have the same electrical charge, spin and magnetic moment as real electrons but may have a different mass.^[121] When free electrons—both in vacuum and metals—move, they produce a net flow of charge called an electric current, which generates a magnetic field. Likewise a current can be created by a changing magnetic field. These interactions are described mathematically by Maxwell's equations.^[122]

At a given temperature, each material has an electrical conductivity that determines the value of electric current when an electric potential is applied. Examples of good conductors include metals such as copper and gold, whereas glass and Teflon are poor conductors. In any dielectric material, the electrons remain bound to their respective atoms and the material behaves as an insulator. Most semiconductors have a variable level of conductivity that lies between the extremes of conduction and insulation.^[123] On the other hand, metals have an electronic band structure containing partially filled electronic bands. The presence of such bands allows electrons in metals to behave as if they were free or delocalized electrons. These electrons are not associated with specific atoms, so when an electric field is applied, they are free to move like a gas (called Fermi gas)^[124] through the material much like free electrons.

Because of collisions between electrons and atoms, the drift velocity of electrons in a conductor is on the order of millimeters per second. However, the speed at which a change of current at one point in the material causes changes in currents in other parts of the material, the velocity of propagation, is typically about 75% of light speed.^[125] This occurs because electrical signals propagate as a wave, with the velocity dependent on the dielectric constant of the material.^[126]

Metals make relatively good conductors of heat, primarily because the delocalized electrons are free to transport thermal energy between atoms. However, unlike electrical conductivity, the thermal conductivity of a metal is nearly independent of temperature. This is expressed mathematically by the Wiedemann-Franz law,^[124] which states that the ratio of thermal conductivity to the electrical conductivity is proportional to the temperature. The thermal



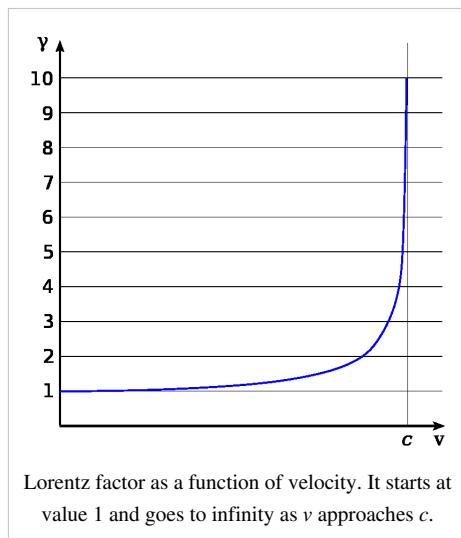
disorder in the metallic lattice increases the electrical resistivity of the material, producing a temperature dependence for electrical current.^[127]

When cooled below a point called the critical temperature, materials can undergo a phase transition in which they lose all resistivity to electrical current, in a process known as superconductivity. In BCS theory, this behavior is modeled by pairs of electrons entering a quantum state known as a Bose–Einstein condensate. These Cooper pairs have their motion coupled to nearby matter via lattice vibrations called phonons, thereby avoiding the collisions with atoms that normally create electrical resistance.^[128] (Cooper pairs have a radius of roughly 100 nm, so they can overlap each other.)^[129] However, the mechanism by which higher temperature superconductors operate remains uncertain.

Electrons inside conducting solids, which are quasi-particles themselves, when tightly confined at temperatures close to absolute zero, behave as though they had split into two other quasiparticles: spinons and holons.^{[130] [131]} The former carries spin and magnetic moment, while the latter electrical charge.

Motion and energy

According to Einstein's theory of special relativity, as an electron's speed approaches the speed of light, from an observer's point of view its relativistic mass increases, thereby making it more and more difficult to accelerate it from within the observer's frame of reference. The speed of an electron can approach, but never reach, the speed of light in a vacuum, c . However, when relativistic electrons—that is, electrons moving at a speed close to c —are injected into a dielectric medium such as water, where the local speed of light is significantly less than c , the electrons temporarily travel faster than light in the medium. As they interact with the medium, they generate a faint light called Cherenkov radiation.^[132]



The effects of special relativity are based on a quantity known as the Lorentz factor, defined as $\gamma = 1/\sqrt{1-v^2/c^2}$ where v is the speed of the particle. The kinetic energy K_e of an electron moving with velocity v is:

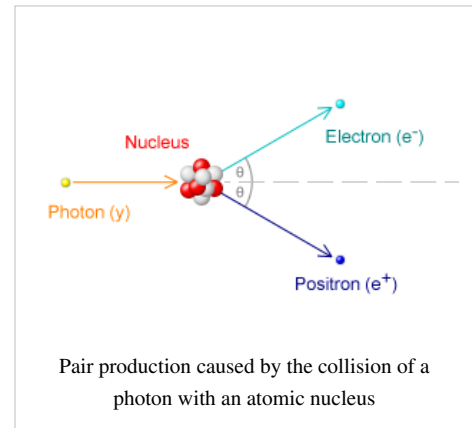
$$K_e = (\gamma - 1)m_e c^2,$$

where m is the mass of electron. For example, the Stanford linear accelerator can accelerate an electron to roughly 51 GeV.^[133] This gives a value of nearly 100,000 for γ , since the mass of an electron is $0.51 \text{ MeV}/c^2$. The relativistic momentum of this electron is 100,000 times the momentum that classical mechanics would predict for an electron at the same speed.^[134]

Since an electron behaves as a wave, at a given velocity it has a characteristic de Broglie wavelength. This is given by $\lambda_e = h/p$ where h is the Planck constant and p is the momentum.^[50] For the 51 GeV electron above, the wavelength is about $2.4 \times 10^{-17} \text{ m}$, small enough to explore structures well below the size of an atomic nucleus.^[135]

Formation

The Big Bang theory is the most widely accepted scientific theory to explain the early stages in the evolution of the Universe.^[136] For the first millisecond of the Big Bang, the temperatures were over 10 billion kelvins and photons had mean energies over a million electronvolts. These photons were sufficiently energetic that they could react with each other to form pairs of electrons and positrons,



$$\gamma + \gamma \rightleftharpoons e^+ + e^-,$$

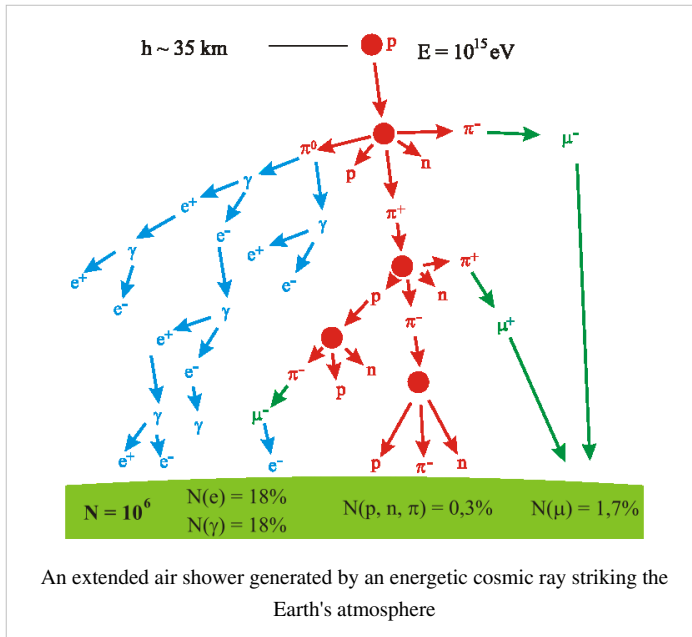
where γ is a photon, e^+ is a positron and e^- is an electron. Likewise, positron-electron pairs annihilated each other and emitted energetic photons. An equilibrium between electrons, positrons and photons was maintained during this phase of the evolution of the Universe. After 15 seconds had passed, however, the temperature of the universe dropped below the threshold where electron-positron formation could occur. Most of the surviving electrons and positrons annihilated each other, releasing gamma radiation that briefly reheated the universe.^[137]

For reasons that remain uncertain, during the process of leptogenesis there was an excess in the number of electrons over positrons.^[138] Hence, about one electron in every billion survived the annihilation process. This excess matched the excess of protons over anti-protons, in a condition known as baryon asymmetry, resulting in a net charge of zero for the universe.^{[139] [140]} The surviving protons and neutrons began to participate in reactions with each other—in the process known as nucleosynthesis, forming isotopes of hydrogen and helium, with trace amounts of lithium. This process peaked after about five minutes.^[141] Any leftover neutrons underwent negative beta decay with a half-life of about a thousand seconds, releasing a proton and electron in the process,

$$n \Rightarrow p + e^- + \bar{\nu}_e,$$

where n is a neutron, p is a proton and $\bar{\nu}_e$ is an electron antineutrino. For about the next 300,000–400,000 years, the excess electrons remained too energetic to bind with atomic nuclei.^[142] What followed is a period known as recombination, when neutral atoms were formed and the expanding universe became transparent to radiation.^[143]

Roughly one million years after the big bang, the first generation of stars began to form.^[143] Within a star, stellar nucleosynthesis results in the production of positrons from the fusion of atomic nuclei. These antimatter particles immediately annihilate with electrons, releasing gamma rays. The net result is a steady reduction in the number of electrons, and a matching increase in the number of neutrons. However, the process of stellar evolution can result in the synthesis of radioactive isotopes. Selected isotopes can subsequently undergo negative beta decay, emitting an electron and antineutrino from the nucleus.^[144] An example is the cobalt-60 (^{60}Co) isotope, which decays to form nickel-60 (^{60}Ni).^[145]



At the end of its lifetime, a star with more than about 20 solar masses can undergo gravitational collapse to form a black hole.^[146] According to classical physics, these massive stellar objects exert a gravitational attraction that is strong enough to prevent anything, even electromagnetic radiation, from escaping past the Schwarzschild radius. However, it is believed that quantum mechanical effects may allow Hawking radiation to be emitted at this distance. Electrons (and positrons) are thought to be created at the event horizon of these stellar remnants.

When pairs of virtual particles (such as an electron and positron) are created in the vicinity of the event horizon, the random spatial

distribution of these particles may permit one of them to appear on the exterior; this process is called quantum tunneling. The gravitational potential of the black hole can then supply the energy that transforms this virtual particle into a real particle, allowing it to radiate away into space.^[147] In exchange, the other member of the pair is given negative energy, which results in a net loss of mass-energy by the black hole. The rate of Hawking radiation increases with decreasing mass, eventually causing the black hole to evaporate away until, finally, it explodes.^[148]

Cosmic rays are particles traveling through space with high energies. Energy events as high as 3.0×10^{20} eV have been recorded.^[149] When these particles collide with nucleons in the Earth's atmosphere, a shower of particles is generated, including pions.^[150] More than half of the cosmic radiation observed from the Earth's surface consists of muons. The particle called a muon is a lepton which is produced in the upper atmosphere by the decay of a pion. A muon, in turn, can decay to form an electron or positron. Thus, for the negatively charged pion π^- ,^[151]

$$\pi^- \rightarrow \mu^- + \bar{\nu}_\mu,$$

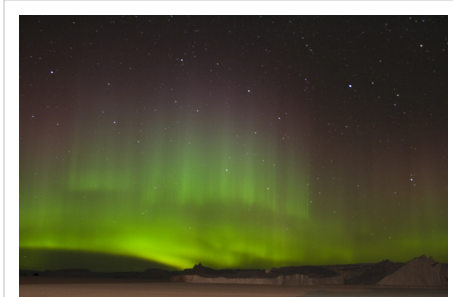
$$\mu^- \rightarrow e^- + \bar{\nu}_e + \nu_\mu,$$

where μ^- is a muon and $\bar{\nu}_\mu$ is a muon neutrino.

Observation

Remote observation of electrons requires detection of their radiated energy. For example, in high-energy environments such as the corona of a star, free electrons form a plasma that radiates energy due to Bremsstrahlung. Electron gas can undergo plasma oscillation, which is waves caused by synchronized variations in electron density, and these produce energy emissions that can be detected by using radio telescopes.^[153]

The frequency of a photon is proportional to its energy. As a bound electron transitions between different energy levels of an atom, it will absorb or emit photons at characteristic frequencies. For instance, when atoms are irradiated by a source with a broad spectrum, distinct absorption lines will appear in the spectrum of transmitted radiation. Each element or molecule displays a characteristic set of spectral lines, such as the hydrogen spectral series. Spectroscopic measurements of the strength and width of these lines allow the composition and



Aurorae are mostly caused by energetic electrons precipitating into the atmosphere.^[152]

physical properties of a substance to be determined.^{[154] [155]}

In laboratory conditions, the interactions of individual electrons can be observed by means of particle detectors, which allow measurement of specific properties such as energy, spin and charge.^[112] The development of the Paul trap and Penning trap allows charged particles to be contained within a small region for long durations. This enables precise measurements of the particle properties. For example, in one instance a Penning trap was used to contain a single electron for a period of 10 months.^[156] The magnetic moment of the electron was measured to a precision of eleven digits, which, in 1980, was a greater accuracy than for any other physical constant.^[157]

The first video images of an electron's energy distribution were captured by a team at Lund University in Sweden, February 2008. The scientists used extremely short flashes of light, called attosecond pulses, which allowed an electron's motion to be observed for the first time.^{[158] [159]}

The distribution of the electrons in solid materials can be visualized by angle resolved photoemission spectroscopy (ARPES). This technique employs the photoelectric effect to measure the reciprocal space—a mathematical representation of periodic structures that is used to infer the original structure. ARPES can be used to determine the direction, speed and scattering of electrons within the material.^[160]

Plasma applications

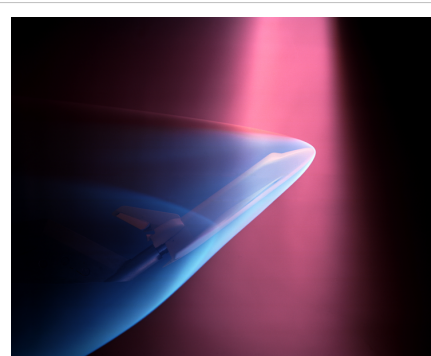
Particle beams

Electron beams are used in welding,^[162] which allows energy densities up to $\times 10^7 \text{ W}\cdot\text{cm}^{-2}$ across a narrow focus diameter of 0.1–1.3 mm and usually does not require a filler material. This welding technique must be performed in a vacuum, so that the electron beam does not interact with the gas prior to reaching the target, and it can be used to join conductive materials that would otherwise be considered unsuitable for welding.^{[163] [164]}

Electron beam lithography (EBL) is a method of etching semiconductors at resolutions smaller than a micron.^[165] This technique is limited by high costs, slow performance, the need to operate the beam in the vacuum and the tendency of the electrons to scatter in solids. The last problem limits the resolution to about 10 nm. For this reason, EBL is primarily used for the production of small numbers of specialized integrated circuits.^[166]

Electron beam processing is used to irradiate materials in order to change their physical properties or sterilize medical and food products.^[167] In radiation therapy, electron beams are generated by linear accelerators for treatment of superficial tumors. Because an electron beam only penetrates to a limited depth before being absorbed, typically up to 5 cm for electron energies in the range 5–20 MeV, electron therapy is useful for treating skin lesions such as basal cell carcinomas. An electron beam can be used to supplement the treatment of areas that have been irradiated by X-rays.^{[168] [169]}

Particle accelerators use electric fields to propel electrons and their antiparticles to high energies. As these particles pass through magnetic fields, they emit synchrotron radiation. The intensity of this radiation is spin dependent, which causes polarization of the electron beam—a process known as the Sokolov–Ternov effect.^[170] The polarized electron beams can be useful for various experiments. Synchrotron radiation can also be used for cooling the electron beams, which reduces the momentum spread of the particles. Once the particles have accelerated to the required energies, separate electron and positron beams are brought into collision. The resulting energy emissions are observed with particle detectors and are studied in particle physics.^[171]



During a NASA wind tunnel test, a model of the Space Shuttle is targeted by a beam of electrons, simulating the effect of ionizing gases during re-entry.^[161]

Imaging

Low-energy electron diffraction (LEED) is a method of bombarding a crystalline material with a collimated beam of electrons, then observing the resulting diffraction patterns to determine the structure of the material. The required energy of the electrons is typically in the range 20–200 eV.^[172] The reflection high energy electron diffraction (RHEED) technique uses the reflection of a beam of electrons fired at various low angles to characterize the surface of crystalline materials. The beam energy is typically in the range 8–20 keV and the angle of incidence is 1–4°.^[173]^[174]

The electron microscope directs a focused beam of electrons at a specimen. As the beam interacts with the material, some electrons change their properties, such as movement direction, angle, relative phase and energy. By recording these changes in the electron beam, microscopists can produce atomically resolved image of the material.^[175] In blue light, conventional optical microscopes have a diffraction-limited resolution of about 200 nm.^[176] By comparison, electron microscopes are limited by the de Broglie wavelength of the electron. This wavelength, for example, is equal to 0.0037 nm for electrons accelerated across a 100,000-volt potential.^[177] The Transmission Electron Aberration-corrected Microscope is capable of sub-0.05 nm resolution, which is more than enough to resolve individual atoms.^[178] This capability makes the electron microscope a useful laboratory instrument for high resolution imaging. However, electron microscopes are expensive instruments that are costly to maintain.

There are two main types of electron microscopes: transmission and scanning. Transmission electron microscopes function in a manner similar to overhead projector, with a beam of electrons passing through a slice of material then being projected by lenses on a photographic slide or a charge-coupled device. In scanning electron microscopes, the image is produced by rastering a finely focused electron beam, as in a TV set, across the studied sample. The magnifications range from 100× to 1,000,000× or higher for both microscope types. The scanning tunneling microscope uses quantum tunneling of electrons from a sharp metal tip into the studied material and can produce atomically resolved images of its surface.^[179]^[180]^[181]

Other

In the free electron laser (FEL), a relativistic electron beam is passed through a pair of undulators containing arrays of dipole magnets, whose fields are oriented in alternating directions. The electrons emit synchrotron radiation, which, in turn, coherently interacts with the same electrons. This leads to the strong amplification of the radiation field at the resonance frequency. FEL can emit a coherent high-brilliance electromagnetic radiation with a wide range of frequencies, from microwaves to soft X-rays. These devices can be used in the future for manufacturing, communication and various medical applications, such as soft tissue surgery.^[182]

Electrons are at the heart of cathode ray tubes, which are used extensively as display devices in laboratory instruments, computer monitors and television sets.^[183] In a photomultiplier tube, every photon striking the photocathode initiates an avalanche of electrons that produces a detectable current pulse.^[184] Vacuum tubes use the flow of electrons to manipulate electrical signals, and they played a critical role in the development of electronics technology. However, they have been largely supplanted by solid-state devices such as the transistor.^[185]

Notes

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$$S = \sqrt{s(s+1)} \cdot \frac{h}{2\pi}$$

$$= \frac{\sqrt{3}}{2} \hbar$$

for quantum number $s = \frac{1}{2}$.

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$$\mu_B = \frac{e\hbar}{2m_e}$$

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From electrostatics theory, the potential energy of a sphere with radius r and charge e is given by:

$$E_p = \frac{e^2}{8\pi\epsilon_0 r},$$

where ϵ_0 is the vacuum permittivity. For an electron with rest mass m_0 , the rest energy is equal to:

$$E_p = m_0 c^2,$$

where c is the speed of light in a vacuum. Setting them equal and solving for r gives the classical electron radius.

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$$v = c\sqrt{1 - \gamma^{-2}}$$

$$= 0.999\,999\,999\,95\,c.$$

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Algebraic quantum field theory

The **Haag-Kastler** axiomatic framework for quantum field theory, named after Rudolf Haag and Daniel Kastler, is an application to *local* quantum physics of C^* -algebra theory. It is therefore also known as **Algebraic Quantum Field Theory** (AQFT). The axioms are stated in terms of an algebra given for every open set in Minkowski space, and mappings between those.

Let **Mink** be the category of open subsets of Minkowski space M with inclusion maps as morphisms. We are given a covariant functor $\mathcal{A}$ from **Mink** to **uC*alg**, the category of unital C^* algebras, such that every morphism in **Mink** maps to a monomorphism in **uC*alg** (*isotony*).

The Poincaré group acts continuously on **Mink**. There exists a pullback of this action, which is continuous in the norm topology of $\mathcal{A}(M)$ (Poincaré covariance).

Minkowski space has a causal structure. If an open set V lies in the causal complement of an open set U , then the image of the maps

$$\mathcal{A}(i_{U,U \cup V})$$

and

$$\mathcal{A}(i_{V,U \cup V})$$

commute (spacelike commutativity). If $\bar{U}$ is the causal completion of an open set U , then $\mathcal{A}(i_{U,\bar{U}})$ is an isomorphism (primitive causality).

A state with respect to a C^* -algebra is a positive linear functional over it with unit norm. If we have a state over $\mathcal{A}(M)$, we can take the "partial trace" to get states associated with $\mathcal{A}(U)$ for each open set via the net monomorphism. It's easy to show the states over the open sets form a presheaf structure.

According to the GNS construction, for each state, we can associate a Hilbert space representation of $\mathcal{A}(M)$. Pure states correspond to irreducible representations and mixed states correspond to reducible representations. Each irreducible (up to equivalence) is called a superselection sector. We assume there is a pure state called the vacuum such that the Hilbert space associated with it is a unitary representation of the Poincaré group compatible with the Poincaré covariance of the net such that if we look at the Poincaré algebra, the spectrum with respect to energy-momentum (corresponding to spacetime translations) lies on and in the positive light cone. This is the vacuum sector.

Suggested reading

- Haag, Rudolf (1992). *Local Quantum Physics: Fields, Particles, Algebras*. Springer.

External links

- Local Quantum Physics Crossroads ^[1] - A network of scientists working on Local Quantum Physics
- Algebraic Quantum Field Theory ^[2] - AQFT resources at the University of Hamburg

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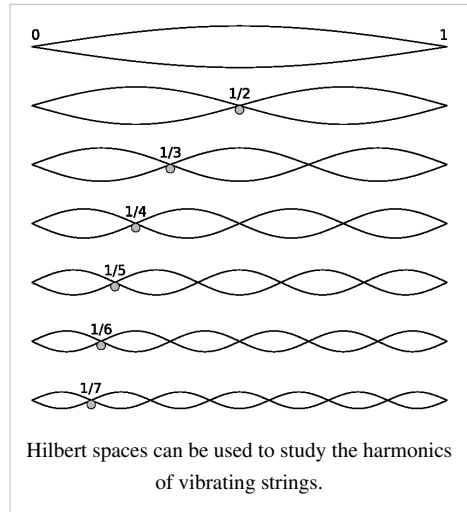
- [1] <http://www.lqp.uni-goettingen.de/>
 [2] <http://unith.desy.de/research/aqft/>

Hilbert space

The mathematical concept of a **Hilbert space**, named after David Hilbert, generalizes the notion of Euclidean space. It extends the methods of vector algebra and calculus from the two-dimensional Euclidean plane and three-dimensional space to spaces with any finite or infinite number of dimensions. A Hilbert space is an abstract vector space possessing the structure of an inner product that allows length and angle to be measured. Furthermore, Hilbert spaces are required to be complete, a property that stipulates the existence of enough limits in the space to allow the techniques of calculus to be used.

Hilbert spaces arise naturally and frequently in mathematics, physics, and engineering, typically as infinite-dimensional function spaces. The earliest Hilbert spaces were studied from this point of view in the first decade of the 20th century by David Hilbert, Erhard Schmidt, and Frigyes Riesz. They are indispensable tools in the theories of partial differential equations, quantum mechanics, Fourier analysis (which includes applications to signal processing and heat transfer) and ergodic theory which forms the mathematical underpinning of the study of thermodynamics. John von Neumann coined the term "Hilbert space" for the abstract concept underlying many of these diverse applications. The success of Hilbert space methods ushered in a very fruitful era for functional analysis. Apart from the classical Euclidean spaces, examples of Hilbert spaces include spaces of square-integrable functions, spaces of sequences, Sobolev spaces consisting of generalized functions, and Hardy spaces of holomorphic functions.

Geometric intuition plays an important role in many aspects of Hilbert space theory. Exact analogs of the Pythagorean theorem and parallelogram law hold in a Hilbert space. At a deeper level, perpendicular projection onto a subspace (the analog of "dropping the altitude" of a triangle) plays a significant role in optimization problems and other aspects of the theory. An element of a Hilbert space can be uniquely specified by its coordinates with respect to a set of coordinate axes (an orthonormal basis), in analogy with Cartesian coordinates in the plane. When that set of axes is countably infinite, this means that the Hilbert space can also usefully be thought of in terms of infinite sequences that are square-summable. Linear operators on a Hilbert space are likewise fairly concrete objects: in good cases, they are simply transformations that stretch the space by different factors in mutually perpendicular directions in a sense that is made precise by the study of their spectral theory.



Definition and illustration

Motivating example: Euclidean space

One of the most familiar examples of a Hilbert space is the Euclidean space consisting of three-dimensional vectors, denoted by $\mathbf{R}^3$, and equipped with the dot product. The dot product takes two vectors $\mathbf{x}$ and $\mathbf{y}$, and produces a real number $\mathbf{x} \cdot \mathbf{y}$. If $\mathbf{x}$ and $\mathbf{y}$ are represented in Cartesian coordinates, then the dot product is defined by

$$(x_1, x_2, x_3) \cdot (y_1, y_2, y_3) = x_1 y_1 + x_2 y_2 + x_3 y_3.$$

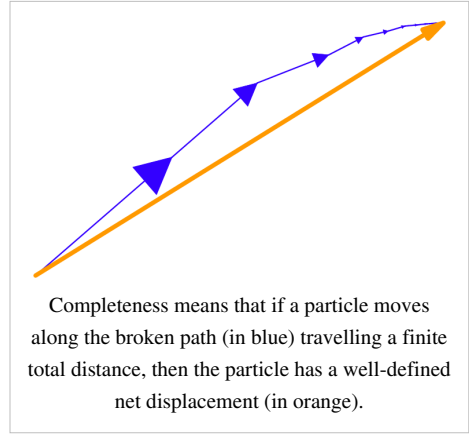
The dot product satisfies the properties:

1. It is symmetric in $\mathbf{x}$ and $\mathbf{y}$: $\mathbf{x} \cdot \mathbf{y} = \mathbf{y} \cdot \mathbf{x}$.
2. It is linear in its first argument: $(a\mathbf{x}_1 + b\mathbf{x}_2) \cdot \mathbf{y} = a\mathbf{x}_1 \cdot \mathbf{y} + b\mathbf{x}_2 \cdot \mathbf{y}$ for any scalars a, b , and vectors $\mathbf{x}_1, \mathbf{x}_2$, and $\mathbf{y}$.
3. It is positive definite: for all vectors $\mathbf{x}$, $\mathbf{x} \cdot \mathbf{x} \geq 0$ with equality if and only if $\mathbf{x} = 0$.

An operation on pairs of vectors that, like the dot product, satisfies these three properties is known as a (real) inner product. A vector space equipped with such an inner product is known as a (real) inner product space. Every finite-dimensional inner product space is also a Hilbert space. The basic feature of the dot product that connects it with Euclidean geometry is that it is related to both the length (or norm) of a vector, denoted $\|\mathbf{x}\|$, and to the angle θ between two vectors $\mathbf{x}$ and $\mathbf{y}$ by means of the formula

$$\mathbf{x} \cdot \mathbf{y} = \|\mathbf{x}\| \|\mathbf{y}\| \cos \theta.$$

Multivariable calculus in Euclidean space relies on the ability to compute limits, and to have useful criteria for concluding that limits exist. A mathematical series



$$\sum_{n=0}^{\infty} \mathbf{x}_n$$

consisting of vectors in $\mathbf{R}^3$ is absolutely convergent provided that the sum of the lengths converges as an ordinary series of real numbers:^[1]

$$\sum_{k=0}^{\infty} \|\mathbf{x}_k\| < \infty.$$

Just as with a series of scalars, a series of vectors that converges absolutely also converges to some limit vector $\mathbf{L}$ in the Euclidean space, in the sense that

$$\left\| \mathbf{L} - \sum_{k=0}^N \mathbf{x}_k \right\| \rightarrow 0 \quad \text{as } N \rightarrow \infty.$$

This property expresses the *completeness* of Euclidean space: that a series which converges absolutely also converges in the ordinary sense.

Definition

A **Hilbert space** H is a real or complex inner product space that is also a complete metric space with respect to the distance function induced by the inner product.^[2] To say that H is a complex inner product space means that H is a complex vector space on which there is an inner product $\langle x, y \rangle$ associating a complex number to each pair of elements x, y of H that satisfies the following properties:

- $\langle y, x \rangle$ is the complex conjugate of $\langle x, y \rangle$:

$$\langle y, x \rangle = \overline{\langle x, y \rangle}.$$

- $\langle x, y \rangle$ is linear in its first argument.^[3] For all complex numbers a and b ,

$$\langle ax_1 + bx_2, y \rangle = a\langle x_1, y \rangle + b\langle x_2, y \rangle.$$

- The inner product is positive definite:

$$\langle x, x \rangle \geq 0$$

where the case of equality holds precisely when $x = 0$.

It follows from properties 1 and 2 that a complex inner product is antilinear in its second argument, meaning that

$$\langle x, ay_1 + by_2 \rangle = \bar{a}\langle x, y_1 \rangle + \bar{b}\langle x, y_2 \rangle.$$

A real inner product space is defined in the same way, except that H is a real vector space and the inner product takes real values. Such an inner product will be bilinear: that is, linear in each argument.

The norm defined by the inner product $\langle \bullet, \bullet \rangle$ is the real-valued function

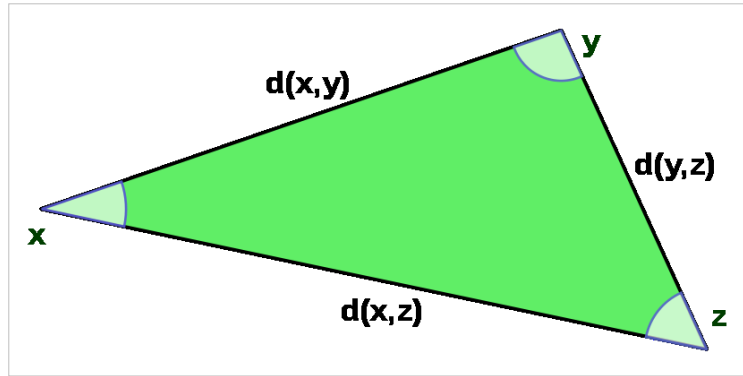
$$\|x\| = \sqrt{\langle x, x \rangle},$$

and the distance between two points x, y in H is defined in terms of the norm by

$$d(x, y) = \|x - y\| = \sqrt{\langle x - y, x - y \rangle}.$$

That this function is a distance function means (1) that it is symmetric in x and y , (2) that the distance between x and itself is zero, and otherwise the distance between x and y must be positive, and (3) that the triangle inequality holds, meaning that the length of one leg of a triangle xyz cannot exceed the sum of the lengths of the other two legs:

$$d(x, z) \leq d(x, y) + d(y, z).$$



This last property is ultimately a consequence of the more fundamental Cauchy–Schwarz inequality, which asserts

$$|\langle x, y \rangle| \leq \|x\| \|y\|$$

with equality if and only if x and y are linearly dependent.

Relative to a distance function defined in this way, any inner product space is a metric space, and sometimes is known as a **pre-Hilbert space**.^[4] A pre-Hilbert space is a Hilbert space if in addition it is complete. Completeness is expressed using a form of the Cauchy criterion for sequences in H : a pre-Hilbert space H is complete if every Cauchy sequence converges with respect to this norm to an element in the space. Completeness can be characterized by the following equivalent condition: if a series of vectors $\sum_{k=0}^{\infty} u_k$ converges absolutely in the sense that

$$\sum_{k=0}^{\infty} \|u_k\| < \infty,$$

then the series converges in H , in the sense that the partial sums converge to an element of H .

As a complete normed space, Hilbert spaces are by definition also Banach spaces. As such they are topological vector spaces, in which topological notions like the openness and closedness of subsets are well-defined. Of special importance is the notion of a closed linear subspace of a Hilbert space which, with the inner product induced by restriction, is also complete (being a closed set in a complete metric space) and therefore a Hilbert space in its own right.

Second example: sequence spaces

The sequence space ℓ^2 consists of all infinite sequences $\mathbf{z} = (z_1, z_2, \dots)$ of complex numbers such that the series

$$\sum_{n=1}^{\infty} |z_n|^2$$

converges. The inner product on ℓ^2 is defined by

$$\langle \mathbf{z}, \mathbf{w} \rangle = \sum_{n=1}^{\infty} z_n \overline{w_n},$$

with the latter series converging as a consequence of the Cauchy–Schwarz inequality.

Completeness of the space holds provided that whenever a series of elements from ℓ^2 converges absolutely (in norm), then it converges to an element of ℓ^2 . The proof is basic in mathematical analysis, and permits mathematical series of elements of the space to be manipulated with the same ease as series of complex numbers (or vectors in a finite-dimensional Euclidean space).^[5]

History

Prior to the development of Hilbert spaces, other generalizations of Euclidean spaces were known to mathematicians and physicists. In particular, the idea of an abstract linear space had gained some traction towards the end of the 19th century:^[6] this is a space whose elements can be added together and multiplied by scalars (such as real or complex numbers) without necessarily identifying these elements with "geometric" vectors, such as position and momentum vectors in physical systems. Other objects studied by mathematicians at the turn of the 20th century, in particular spaces of sequences (including series) and spaces of functions,^[7] can naturally be thought of as linear spaces. Functions, for instance, can be added together or multiplied by constant scalars, and these operations obey the algebraic laws satisfied by addition and scalar multiplication of spatial vectors.

In the first decade of the 20th century, parallel developments led to the introduction of Hilbert spaces. The first of these was the observation, which arose during David Hilbert and Erhard Schmidt's study of integral equations,^[8] that two square-integrable real-valued functions f and g on an interval $[a, b]$ have an *inner product*

$$\langle f, g \rangle = \int_a^b f(x)g(x) dx$$

which has many of the familiar properties of the Euclidean dot product. In particular, the idea of an orthogonal family of functions has meaning. Schmidt exploited the similarity of this inner product with the usual dot product to prove an analog of the spectral decomposition for an operator of the form

$$f(x) \mapsto \int_a^b K(x, y)f(y) dy$$

where K is a continuous function symmetric in x and y . The resulting eigenfunction expansion expresses the function K as a series of the form

$$K(x, y) = \sum_n \lambda_n \varphi_n(x) \varphi_n(y)$$



David Hilbert

where the functions φ_n are orthogonal in the sense that $\langle \varphi_n, \varphi_m \rangle = 0$ for all $n \neq m$. The individual terms in this series are sometimes referred to as elementary product solutions. However, there are eigenfunction expansions which fail to converge in a suitable sense to a square-integrable function: the missing ingredient, which ensures convergence, is completeness.^[9]

The second development was the Lebesgue integral, an alternative to the Riemann integral introduced by Henri Lebesgue in 1904.^[10] The Lebesgue integral made it possible to integrate a much broader class of functions. In 1907, Frigyes Riesz and Ernst Sigismund Fischer independently proved that the space L^2 of square Lebesgue-integrable functions is a complete metric space.^[11] As a consequence of the interplay between geometry and completeness, the 19th century results of Joseph Fourier, Friedrich Bessel and Marc-Antoine Parseval on trigonometric series easily carried over to these more general spaces, resulting in a geometrical and analytical apparatus now usually known as the Riesz-Fischer theorem.^[12]

Further basic results were proved in the early 20th century. For example, the Riesz representation theorem was independently established by Maurice Fréchet and Frigyes Riesz in 1907.^[13] John von Neumann coined the term *abstract Hilbert space* in his work on unbounded Hermitian operators.^[14] Although other mathematicians such as Hermann Weyl and Norbert Wiener had already studied particular Hilbert spaces in great detail, often from a physically-motivated point of view, von Neumann gave the first complete and axiomatic treatment of them.^[15] Von Neumann later used them in his seminal work on the foundations of quantum mechanics,^[16] and in his continued work with Eugene Wigner. The name "Hilbert space" was soon adopted by others, for example by Hermann Weyl in his book on quantum mechanics and the theory of groups.^[17]

The significance of the concept of a Hilbert space was underlined with the realization that it offers one of the best mathematical formulations of quantum mechanics.^[18] In short, the states of a quantum mechanical system are vectors in a certain Hilbert space, the observables are hermitian operators on that space, the symmetries of the system are unitary operators, and measurements are orthogonal projections. The relation between quantum mechanical symmetries and unitary operators provided an impetus for the development of the unitary representation theory of groups, initiated in the 1928 work of Hermann Weyl.^[17] On the other hand, in the early 1930s it became clear that certain properties of classical dynamical systems can be analyzed using Hilbert space techniques in the framework of ergodic theory.^[19]

The algebra of observables in quantum mechanics is naturally an algebra of operators defined on a Hilbert space, according to Werner Heisenberg's matrix mechanics formulation of quantum theory. Von Neumann began investigating operator algebras in the 1930s, as rings of operators on a Hilbert space. The kind of algebras studied by von Neumann and his contemporaries are now known as von Neumann algebras. In the 1940s, Israel Gelfand, Mark Naimark and Irving Segal gave a definition of a kind of operator algebras called C*-algebras that on the one hand made no reference to an underlying Hilbert space, and on the other extrapolated many of the useful features of the operator algebras that had previously been studied. The spectral theorem for self-adjoint operators in particular that underlies much of the existing Hilbert space theory was generalized to C*-algebras. These techniques are now basic in abstract harmonic analysis and representation theory.

Examples

Lebesgue spaces

Lebesgue spaces are function spaces associated to measure spaces (X, M, μ) , where X is a set, M is a σ -algebra of subsets of X , and μ is a countably additive measure on M . Let $L^2(X, \mu)$ be the space of those complex-valued measurable functions on X for which the Lebesgue integral of the square of the absolute value of the function is finite, i.e., for a function f in $L^2(X, \mu)$,

$$\int_X |f|^2 d\mu < \infty,$$

and where functions are identified if and only if they differ only on a set of measure zero.

The inner product of functions f and g in $L^2(X, \mu)$ is then defined as

$$\langle f, g \rangle = \int_X f(t) \overline{g(t)} d\mu(t).$$

For f and g in L^2 , this integral exists because of the Cauchy–Schwarz inequality, and defines an inner product on the space. Equipped with this inner product, L^2 is in fact complete.^[20] The Lebesgue integral is essential to ensure completeness: on domains of real numbers, for instance, not enough functions are Riemann integrable.^[21]

The Lebesgue spaces appear in many natural settings. The spaces $L^2(\mathbf{R})$ and $L^2([0,1])$ of square-integrable functions with respect to the Lebesgue measure on the real line and unit interval, respectively, are natural domains on which to define the Fourier transform and Fourier series. In other situations, the measure may be something other than the ordinary Lebesgue measure on the real line. For instance, if w is any positive measurable function, the space of all measurable functions f on the interval $[0,1]$ satisfying

$$\int_0^1 |f(t)|^2 w(t) dt < \infty$$

is called the weighted L^2 space $L^2_{w, \mu}([0,1])$, and w is called the weight function. The inner product is defined by

$$\langle f, g \rangle = \int_0^1 f(t) \overline{g(t)} w(t) dt.$$

The weighted space $L^2_{w, \mu}([0,1])$ is identical with the Hilbert space $L^2([0,1], \mu)$ where the measure μ of a Lebesgue-measurable set A is defined by

$$\mu(A) = \int_A w(t) dt.$$

Weighted L^2 spaces like this are frequently used to study orthogonal polynomials, because different families of orthogonal polynomials are orthogonal with respect to different weighting functions.

Sobolev spaces

Sobolev spaces, denoted by H^s or $W^{s,2}$, are Hilbert spaces. These are a special kind of function space in which differentiation may be performed, but which (unlike other Banach spaces such as the Hölder spaces) support the structure of an inner product. Because differentiation is permitted, Sobolev spaces are a convenient setting for the theory of partial differential equations.^[22] They also form the basis of the theory of direct methods in the calculus of variations.^[23]

For s a non-negative integer and $\Omega \subset \mathbf{R}^n$, the Sobolev space $H^s(\Omega)$ contains L^2 functions whose weak derivatives of order up to s are also L^2 . The inner product in $H^s(\Omega)$ is

$$\langle f, g \rangle = \int_{\Omega} f(x) \overline{g(x)} dx + \int_{\Omega} Df \cdot D\overline{g}(x) dx + \dots + \int_{\Omega} D^s f(x) \cdot D^s \overline{g}(x) dx$$

where the dot indicates the dot product in the Euclidean space of partial derivatives of each order. Sobolev spaces can also be defined when s is not an integer.

Sobolev spaces are also studied from the point of view of spectral theory, relying more specifically on the Hilbert space structure. If Ω is a suitable domain, then one can define the Sobolev space $H^s(\Omega)$ as the space of Bessel potentials;^[24] roughly,

$$H^s(\Omega) = \{(1 - \Delta)^{-s/2} f \mid f \in L^2(\Omega)\}.$$

Here Δ is the Laplacian and $(1 - \Delta)^{-s/2}$ is understood in terms of the spectral mapping theorem. Apart from providing a workable definition of Sobolev spaces for non-integer s , this definition also has particularly desirable properties under the Fourier transform that make it ideal for the study of pseudodifferential operators. Using these methods on a compact Riemannian manifold, one can obtain for instance the Hodge decomposition which is the basis of Hodge theory.^[25]

Spaces of holomorphic functions

Hardy spaces

The Hardy spaces are function spaces, arising in complex analysis and harmonic analysis, whose elements are certain holomorphic functions in a complex domain.^[26] Let U denote the unit disc in the complex plane. Then the Hardy space $H^2(U)$ is defined to be the space of holomorphic functions f on U such that the means

$$M_r(f) = \frac{1}{2\pi} \int_0^{2\pi} |f(re^{i\theta})|^2 d\theta$$

remain bounded for $r < 1$. The norm on this Hardy space is defined by

$$\|f\|_2 = \lim_{r \rightarrow 1} \sqrt{M_r(f)}.$$

Hardy spaces in the disc are related to Fourier series. A function f is in $H^2(U)$ if and only if

$$f(z) = \sum_{n=0}^{\infty} a_n z^n$$

where

$$\sum_{n=0}^{\infty} |a_n|^2 < \infty.$$

Thus $H^2(U)$ consists of those functions which are L^2 on the circle, and whose negative frequency Fourier coefficients vanish.

Bergman spaces

The Bergman spaces are another family of Hilbert spaces of holomorphic functions.^[27] Let D be a bounded open set in the complex plane (or a higher dimensional complex space) and let $L^{2,h}(D)$ be the space of holomorphic functions f in D that are also in $L^2(D)$ in the sense that

$$\|f\|^2 = \int_D |f(z)|^2 d\mu(z) < \infty,$$

where the integral is taken with respect to the Lebesgue measure in D . Clearly $L^{2,h}(D)$ is a subspace of $L^2(D)$; in fact, it is a closed subspace, and so a Hilbert space in its own right. This is a consequence of the estimate, valid on compact subsets K of D , that

$$\sup_{z \in K} |f(z)| \leq C_K \|f\|_2,$$

which in turn follows from Cauchy's integral formula. Thus convergence of a sequence of holomorphic functions in $L^2(D)$ implies also compact convergence, and so the limit function is also holomorphic. Another consequence of this inequality is that the linear functional that evaluates a function f at a point of D is actually continuous on $L^{2,h}(D)$. The Riesz representation theorem implies that the evaluation functional can be represented as an element of $L^{2,h}(D)$. Thus, for every $z \in D$, there is a function $\eta_z \in L^{2,h}(D)$ such that

$$f(z) = \int_D f(\zeta) \overline{\eta_z(\zeta)} d\mu(\zeta)$$

for all $f \in L^{2,h}(D)$. The integrand

$$K(\zeta, z) = \overline{\eta_z(\zeta)}$$

is known as the Bergman kernel of D . This integral kernel satisfies a reproducing property

$$f(z) = \int_D f(\zeta) K(\zeta, z) d\mu(\zeta).$$

A Bergman space is an example of a reproducing kernel Hilbert space, which is a Hilbert space of functions along with a kernel $K(\zeta, z)$ that verifies a reproducing property analogous to this one. The Hardy space $H^2(D)$ also admits a reproducing kernel, known as the Szegő kernel.^[28] Reproducing kernels are common in other areas of mathematics as well. For instance, in harmonic analysis the Poisson kernel is a reproducing kernel for the Hilbert space of square-integrable harmonic functions in the unit ball. That the latter is a Hilbert space at all is a consequence of the mean value theorem for harmonic functions.

Applications

Many of the applications of Hilbert spaces exploit the fact that Hilbert spaces support generalizations of simple geometric concepts like projection and change of basis from their usual finite dimensional setting. In particular, the spectral theory of continuous self-adjoint linear operators on a Hilbert space generalizes the usual spectral decomposition of a matrix, and this often plays a major role in applications of the theory to other areas of mathematics and physics.

Sturm–Liouville theory

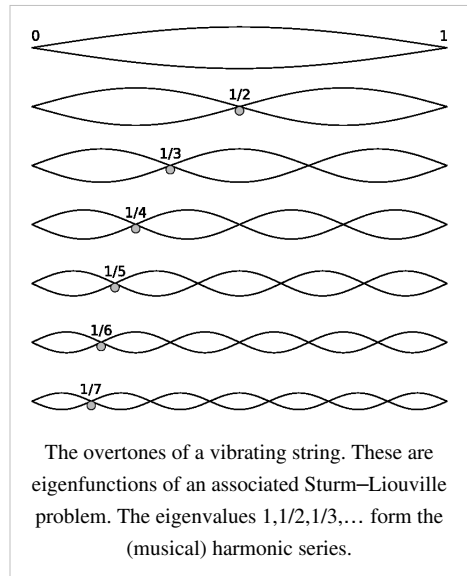
In the theory of ordinary differential equations, spectral methods on a suitable Hilbert space are used to study the behavior of eigenvalues and eigenfunctions of differential equations. For example, the Sturm–Liouville problem arises in the study of the harmonics of waves in a violin string or a drum, and is a central problem in ordinary differential equations.^[29] The problem is a differential equation of the form

$$-\frac{d}{dx} \left[p(x) \frac{dy}{dx} \right] + q(x)y = \lambda w(x)y$$

for an unknown function y on an interval $[a, b]$, satisfying general homogeneous Robin boundary conditions

$$\begin{cases} \alpha y(a) + \alpha' y'(a) = 0 \\ \beta y(b) + \beta' y'(b) = 0. \end{cases}$$

The functions p , q , and w are given in advance, and the problem is to find the function y and constants λ for which the equation has a solution. The problem only has solutions for certain values of λ , called eigenvalues of the system,



and this is a consequence of the spectral theorem for compact operators applied to the integral operator defined by the Green's function for the system. Furthermore, another consequence of this general result is that the eigenvalues λ of the system can be arranged in an increasing sequence tending to infinity.^[30]

Partial differential equations

Hilbert spaces form a basic tool in the study of partial differential equations.^[22] For many classes of partial differential equations, such as linear elliptic equations, it is possible to consider a generalized solution (known as a weak solution) by enlarging the class of functions. Many weak formulations involve the class of Sobolev functions, which is a Hilbert space. A suitable weak formulation reduces to a geometrical problem the analytic problem of finding a solution or, often what is more important, showing that a solution exists and is unique for given boundary data. For linear elliptic equations, one geometrical result that ensures unique solvability for a large class of problems is the Lax–Milgram theorem. This strategy forms the rudiment of the Galerkin method (a finite element method) for numerical solution of partial differential equations.^[31]

A typical example is the Poisson equation $-\Delta u = g$ with Dirichlet boundary conditions in a bounded domain Ω in $\mathbf{R}^2$. The weak formulation consists of finding a function u such that, for all continuously differentiable functions v in Ω vanishing on the boundary:

$$\int_{\Omega} \nabla u \cdot \nabla v = \int_{\Omega} g v.$$

This can be recast in terms of the Hilbert space $H_0^1(\Omega)$ consisting of functions u such that u , along with its weak partial derivatives, are square integrable on Ω , and which vanish on the boundary. The question then reduces to finding u in this space such that for all v in this space

$$a(u, v) = b(v)$$

where a is a continuous bilinear form, and b is a continuous linear functional, given respectively by

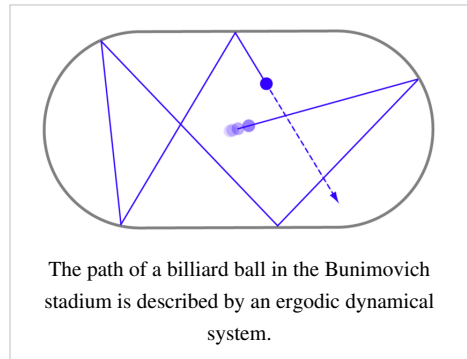
$$a(u, v) = \int_{\Omega} \nabla u \cdot \nabla v, \quad b(v) = \int_{\Omega} g v.$$

Since the Poisson equation is elliptic, it follows from Poincaré's inequality that the bilinear form a is coercive. The Lax–Milgram theorem then ensures the existence and uniqueness of solutions of this equation.

Hilbert spaces allow for many elliptic partial differential equations to be formulated in a similar way, and the Lax–Milgram theorem is then a basic tool in their analysis. With suitable modifications, similar techniques can be applied to parabolic partial differential equations and certain hyperbolic partial differential equations.

Ergodic theory

The field of ergodic theory is the study of the long-term behavior of chaotic dynamical systems. The prototypical case of a field to which ergodic theory is applicable is that of thermodynamics in which, although the microscopic state of a system is extremely complicated—it is impossible to understand the ensemble of individual collisions between particles of matter—the average behavior over sufficiently long time intervals is tractable. The laws of thermodynamics are assertions about such average behavior. In particular, one formulation of the zeroth law of thermodynamics asserts that over sufficiently long timescales, the only functionally independent measurement that one can make of a thermodynamic system in equilibrium is its total energy, in the form of temperature.



An ergodic dynamical system is one for which, apart from the energy—measured by the Hamiltonian—there are no other functionally independent conserved quantities on the phase space. More explicitly, suppose that the energy E is fixed, and let Ω_E be the subset of the phase space consisting of all states of energy E (an energy surface), and let T_t denote the evolution operator on the phase space. The dynamical system is ergodic if there are no continuous non-constant functions on Ω_E such that

$$f(T_t w) = f(w)$$

for all w on Ω_E and all time t . Liouville's theorem implies that there exists a measure μ on the energy surface that is invariant under the time translation. As a result, time translation is a unitary transformation of the Hilbert space $L^2(\Omega_E, \mu)$ consisting of square-integrable functions on the energy surface Ω_E with respect to the inner product

$$\langle f, g \rangle_{L^2(\Omega_E, \mu)} = \int_E f \bar{g} d\mu.$$

The von Neumann mean ergodic theorem^[19] states the following:

- If U_t is a (strongly continuous) one-parameter semigroup of unitary operators on a Hilbert space H , and P is the orthogonal projection onto the space of common fixed points of U_t , $\{x \in H \mid U_t x = x \text{ for all } t > 0\}$, then

$$Px = \lim_{T \rightarrow \infty} \frac{1}{T} \int_0^T U_t x dt.$$

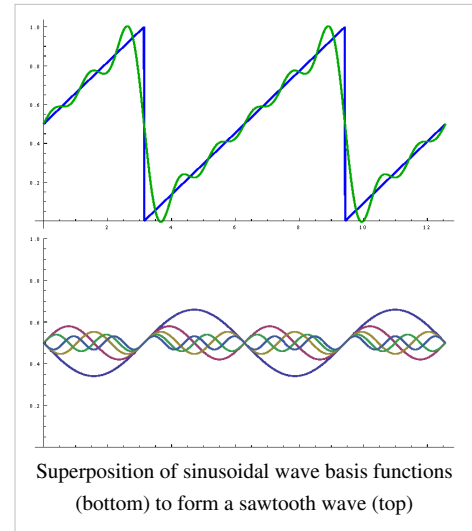
For an ergodic system, the fixed set of the time evolution consists only of the constant functions, so the ergodic theorem implies the following:^[32] for any function $f \in L^2(\Omega_E, \mu)$,

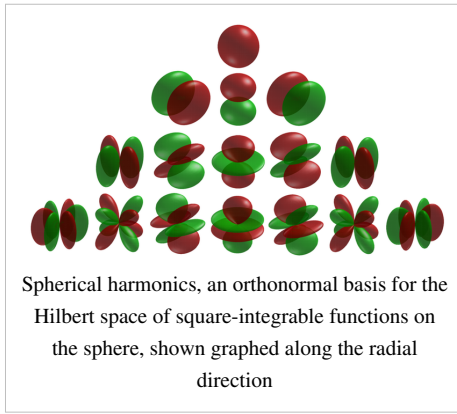
$$L^2\text{-}\lim_{T \rightarrow \infty} \frac{1}{T} \int_0^T f(T_t w) dt = \int_{\Omega_E} f(y) d\mu(y).$$

That is, the long time average of an observable f is equal to its expectation value over an energy surface.

Fourier analysis

One of the basic goals of Fourier analysis is to decompose a function into a (possibly infinite) linear combination of given basis functions: the associated Fourier series. The classical Fourier series associated to a function f defined on the interval $[0,1]$ is a series of the form





$$\sum_{n=-\infty}^{\infty} a_n e^{2\pi i n \theta}$$

where

$$a_n = \int_0^1 f(\theta) e^{-2\pi i n \theta} d\theta.$$

The example of adding up the first few terms in a Fourier series for a sawtooth function is shown in the figure. The basis functions are sine waves with wavelengths λ/n (n =integer) shorter than the wavelength λ of the sawtooth itself (except for $n=1$, the *fundamental* wave). All basis functions have nodes at the nodes of the sawtooth, but all but the fundamental have additional nodes. The oscillation of the summed terms about the sawtooth is called the Gibbs phenomenon.

A significant problem in classical Fourier series asks in what sense the Fourier series converges, if at all, to the function f . Hilbert space methods provide one possible answer to this question.^[33] The functions $e_n(\theta) = e^{2\pi i n \theta}$ form an orthogonal basis of the Hilbert space $L^2([0,1])$. Consequently, any square-integrable function can be expressed as a series

$$f(\theta) = \sum_n a_n e_n(\theta), \quad a_n = \langle f, e_n \rangle$$

and, moreover, this series converges in the Hilbert space sense (that is, in the L^2 mean).

The problem can also be studied from the abstract point of view: every Hilbert space has an orthonormal basis, and every element of the Hilbert space can be written in a unique way as a sum of multiples of these basis elements. The coefficients appearing on these basis elements are sometimes known abstractly as the Fourier coefficients of the element of the space.^[34] The abstraction is especially useful when it is more natural to use different basis functions for a space such as $L^2([0,1])$. In many circumstances, it is desirable not to decompose a function into trigonometric functions, but rather into orthogonal polynomials or wavelets for instance,^[35] and in higher dimensions into spherical harmonics.^[36]

For instance, if e_n are any orthonormal basis functions of $L^2[0,1]$, then a given function in $L^2[0,1]$ can be approximated as a finite linear combination^[37]

$$f(x) \approx f_n(x) = a_1 e_1(x) + a_2 e_2(x) + \cdots + a_n e_n(x)$$

The coefficients $\{a_j\}$ are selected to make the magnitude of the difference $\|f - f_n\|^2$ as small as possible. Geometrically, the best approximation is the orthogonal projection of f onto the subspace consisting of all linear combinations of the $\{e_j\}$, and can be calculated by^[38]

$$a_j = \int_0^1 \overline{e_j(x)} f(x) dx.$$

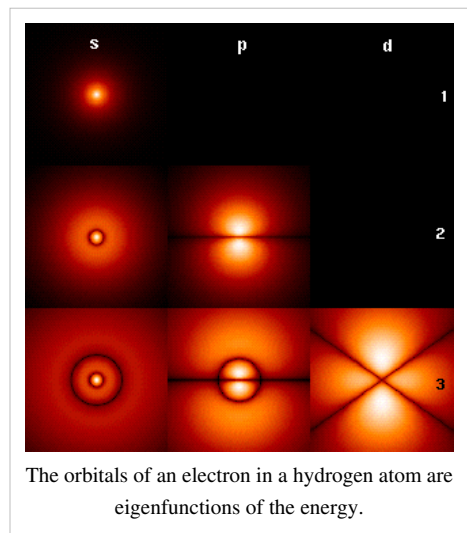
That this formula minimizes the difference $\|f - f_n\|^2$ is a consequence of Bessel's inequality and Parseval's formula.

In various applications to physical problems, a function can be decomposed into physically meaningful eigenfunctions of a differential operator (typically the Laplace operator): this forms the foundation for the spectral study of functions, in reference to the spectrum of the differential operator.^[39] A concrete physical application involves the problem of hearing the shape of a drum: given the fundamental modes of vibration that a drumhead is capable of producing, can one infer the shape of the drum itself?^[40] The mathematical formulation of this question involves the Dirichlet eigenvalues of the Laplace equation in the plane, that represent the fundamental modes of vibration in direct analogy with the integers that represent the fundamental modes of vibration of the violin string.

Spectral theory also underlies certain aspects of the Fourier transform of a function. Whereas Fourier analysis decomposes a function defined on a compact set into the discrete spectrum of the Laplacian (which corresponds to the vibrations of a violin string or drum), the Fourier transform of a function is the decomposition of a function defined on all of Euclidean space into its components in the continuous spectrum of the Laplacian. The Fourier transformation is also geometrical, in a sense made precise by the Plancherel theorem, that asserts that it is an isometry of one Hilbert space (the "time domain") with another (the "frequency domain"). This isometry property of the Fourier transformation is a recurring theme in abstract harmonic analysis, as evidenced for instance by the Plancherel theorem for spherical functions occurring in noncommutative harmonic analysis.

Quantum mechanics

In the mathematically rigorous formulation of quantum mechanics, developed by Paul Dirac^[41] and John von Neumann^[42], the possible states (more precisely, the pure states) of a quantum mechanical system are represented by unit vectors (called *state vectors*) residing in a complex separable Hilbert space, known as the state space, well defined up to a complex number of norm 1 (the phase factor). In other words, the possible states are points in the projectivization of a Hilbert space, usually called the complex projective space. The exact nature of this Hilbert space is dependent on the system; for example, the position and momentum states for a single non-relativistic spin zero particle is the space of all square-integrable functions, while the states for the spin of a single proton are unit elements of the two-dimensional complex Hilbert space of spinors. Each observable is represented by a self-adjoint linear operator acting on the state space. Each eigenstate of an observable corresponds to an eigenvector of the operator, and the associated eigenvalue corresponds to the value of the observable in that eigenstate.



The orbitals of an electron in a hydrogen atom are eigenfunctions of the energy.

The time evolution of a quantum state is described by the Schrödinger equation, in which the Hamiltonian, the operator corresponding to the total energy of the system, generates time evolution.

The inner product between two state vectors is a complex number known as a probability amplitude. During an ideal measurement of a quantum mechanical system, the probability that a system collapses from a given initial state to a particular eigenstate is given by the square of the absolute value of the probability amplitudes between the initial and final states. The possible results of a measurement are the eigenvalues of the operator—which explains the choice of self-adjoint operators, for all the eigenvalues must be real. The probability distribution of an observable in a given state can be found by computing the spectral decomposition of the corresponding operator.

For a general system, states are typically not pure, but instead are represented as statistical mixtures of pure states, or mixed states, given by density matrices: self-adjoint operators of trace one on a Hilbert space. Moreover, for general quantum mechanical systems, the effects of a single measurement can influence other parts of a system in a manner that is described instead by a positive operator valued measure. Thus the structure both of the states and observables

in the general theory is considerably more complicated than the idealization for pure states.

Heisenberg's uncertainty principle is represented by the statement that the operators corresponding to certain observables do not commute, and gives a specific form that the commutator must have.

Properties

Pythagorean identity

Two vectors u and v in a Hilbert space H are orthogonal when $\langle u, v \rangle = 0$. The notation for this is $u \perp v$. More generally, when S is a subset in H , the notation $u \perp S$ means that u is orthogonal to every element from S .

When u and v are orthogonal, one has

$$\|u + v\|^2 = \langle u + v, u + v \rangle = \langle u, u \rangle + 2\operatorname{Re}\langle u, v \rangle + \langle v, v \rangle = \|u\|^2 + \|v\|^2.$$

By induction on n , this is extended to any family $u_1, \dots, u_n$ of n orthogonal vectors,

$$\|u_1 + \dots + u_n\|^2 = \|u_1\|^2 + \dots + \|u_n\|^2.$$

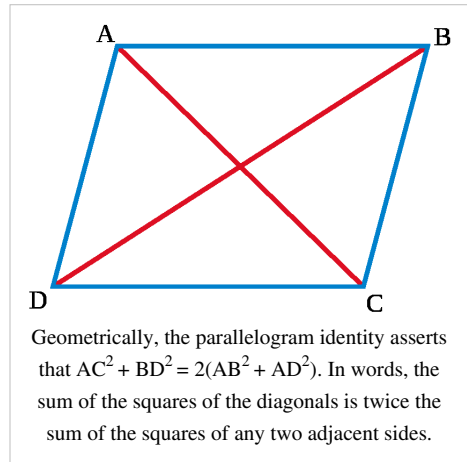
Whereas the Pythagorean identity as stated is valid in any inner product space, completeness is required for the extension of the Pythagorean identity to series. A series $\sum u_k$ of *orthogonal* vectors converges in H if and only if the series of squares of norms converges, and

$$\left\| \sum_{k=0}^{\infty} u_k \right\|^2 = \sum_{k=0}^{\infty} \|u_k\|^2.$$

Furthermore, the sum of a series of orthogonal vectors is independent of the order in which it is taken.

Parallelogram identity and polarization

By definition, every Hilbert space is also a Banach space. Furthermore, in every Hilbert space the following parallelogram identity holds:



$$\|u + v\|^2 + \|u - v\|^2 = 2(\|u\|^2 + \|v\|^2).$$

Conversely, every Banach space in which the parallelogram identity holds is a Hilbert space, and the inner product is uniquely determined by the norm by the polarization identity.^[43] For real Hilbert spaces, the polarization identity is

$$\langle u, v \rangle = \frac{1}{4} (\|u + v\|^2 - \|u - v\|^2).$$

For complex Hilbert spaces, it is

$$\langle u, v \rangle = \frac{1}{4} (\|u + v\|^2 - \|u - v\|^2 + i\|u + iv\|^2 - i\|u - iv\|^2).$$

The parallelogram law implies that any Hilbert space is a uniformly convex Banach space.^[44]

Best approximation

If C is a non-empty closed convex subset of a Hilbert space H and x a point in H , there exists a unique point $y \in C$ which minimizes the distance between x and points in C ,^[45]

$$y \in C, \quad \|x - y\| = \text{dist}(x, C) = \min\{\|x - z\| : z \in C\}.$$

This is equivalent to saying that there is a point with minimal norm in the translated convex set $D = C - x$. The proof consists in showing that every minimizing sequence $(d_n) \subset D$ is Cauchy (using the parallelogram identity) hence converges (using completeness) to a point in D that has minimal norm. More generally, this holds in any uniformly convex Banach space.^[46]

When this result is applied to a closed subspace F of H , it can be shown that the point $y \in F$ closest to x is characterized by^[47]

$$y \in F, \quad x - y \perp F.$$

This point y is the *orthogonal projection* of x onto F , and the mapping $P_F : x \rightarrow y$ is linear (see Orthogonal complements and projections). This result is especially significant in applied mathematics, especially numerical analysis, where it forms the basis of least squares methods.

In particular, when F is not equal to H , one can find a non-zero vector v orthogonal to F (select x not in F and $v = x - y$). A very useful criterion is obtained by applying this observation to the closed subspace F generated by a subset S of H .

A subset S of H spans a dense vector subspace if (and only if) the vector 0 is the sole vector $v \in H$ orthogonal to S .

Duality

The dual space H^* is the space of all continuous linear functions from the space H into the base field. It carries a natural norm, defined by

$$\|\varphi\| = \sup_{\|x\|=1, x \in H} |\varphi(x)|.$$

This norm satisfies the parallelogram law, and so the dual space is also an inner product space. The dual space is also complete, and so it is a Hilbert space in its own right.

The Riesz representation theorem affords a convenient description of the dual. To every element u of H , there is a unique element φ_u of H^* , defined by

$$\varphi_u(x) = \langle x, u \rangle.$$

The mapping $u \mapsto \varphi_u$ is an antilinear mapping from H to H^* . The Riesz representation theorem states that this mapping is an antilinear isomorphism.^[48] Thus to every element φ of the dual H^* there exists one and only one u_φ in H such that

$$\langle x, u_\varphi \rangle = \varphi(x)$$

for all $x \in H$. The inner product on the dual space H^* satisfies

$$\langle \varphi, \psi \rangle = \langle u_\psi, u_\varphi \rangle.$$

The reversal of order on the right-hand side restores linearity in φ from the antilinearity of u_φ . In the real case, the antilinear isomorphism from H to its dual is actually an isomorphism, and so real Hilbert spaces are naturally isomorphic to their own duals.

The representing vector u_φ is obtained in the following way. When $\varphi \neq 0$, the kernel $F = \ker \varphi$ is a closed vector subspace of H , not equal to H , hence there exists a non-zero vector v orthogonal to F . The vector u is a suitable scalar multiple λv of v . The requirement that $\varphi(v) = \langle v, u \rangle$ yields

$$u = \langle v, v \rangle^{-1} \overline{\varphi(v)} v.$$

This correspondence $\varphi \leftrightarrow u$ is exploited by the bra-ket notation popular in physics. It is common in physics to assume that the inner product, denoted by $\langle x|y\rangle$, is linear on the right,

$$\langle x|y\rangle = \langle y, x\rangle.$$

The result $\langle x|y\rangle$ can be seen as the action of the linear functional $\langle x|$ (the *bra*) on the vector $|y\rangle$ (the *ket*).

The Riesz representation theorem relies fundamentally not just on the presence of an inner product, but also on the completeness of the space. In fact, the theorem implies that the topological dual of any inner product space can be identified with its completion. An immediate consequence of the Riesz representation theorem is also that a Hilbert space H is reflexive, meaning that the natural map from H into its double dual space is an isomorphism.

Weakly convergent sequences

In a Hilbert space H , a sequence $\{x_n\}$ is weakly convergent to a vector $x \in H$ when

$$\lim_n \langle x_n, v \rangle = \langle x, v \rangle$$

for every $v \in H$.

For example, any orthonormal sequence $\{f_n\}$ converges weakly to 0, as a consequence of Bessel's inequality. Every weakly convergent sequence $\{x_n\}$ is bounded, by the uniform boundedness principle.

Conversely, every bounded sequence in a Hilbert space admits weakly convergent subsequences (Alaoglu's theorem).^[49] This fact may be used to prove minimization results for continuous convex functionals, in the same way that the Bolzano-Weierstrass theorem is used for continuous functions on $\mathbf{R}^d$. Among several variants, one simple statement is as follows:^[50]

If $f: H \rightarrow \mathbf{R}$ is a convex continuous function such that $f(x)$ tends to $+\infty$ when $\|x\|$ tends to ∞ , then f admits a minimum at some point $x_0 \in H$.

This fact (and its various generalizations) are fundamental for direct methods in the calculus of variations. Minimization results for convex functionals are also a direct consequence of the slightly more abstract fact that closed bounded convex subsets in a Hilbert space H are weakly compact, since H is reflexive. The existence of weakly convergent subsequences is a special case of the Eberlein-Šmulian theorem.

Banach space properties

Any general property of Banach spaces continues to hold for Hilbert spaces. The open mapping theorem states that a continuous surjective linear transformation from one Banach space to another is an open mapping meaning that it sends open sets to open sets. A corollary is the bounded inverse theorem, that a continuous and bijective linear function from one Banach space to another is an isomorphism (that is, a continuous linear map whose inverse is also continuous). This theorem is considerably simpler to prove in the case of Hilbert spaces than in general Banach spaces.^[51] The open mapping theorem is equivalent to the closed graph theorem, which asserts that a function from one Banach space to another is continuous if and only if its graph is a closed set.^[52] In the case of Hilbert spaces, this is basic in the study of unbounded operators (see closed operator).

The (geometrical) Hahn–Banach theorem asserts that a closed convex set can be separated from any point outside it by means of a hyperplane of the Hilbert space. This is an immediate consequence of the best approximation property: if y is the element of a closed convex set F closest to x , then the separating hyperplane is the plane perpendicular to the segment xy passing through its midpoint.^[53]

The distortion problem on Hilbert space asks whether or not every real valued Lipschitz function f defined on the sphere of a separable and infinite dimensional Hilbert space H stabilizes on the sphere of an infinite dimensional subspace, i.e. whether there is a real number $a \in \mathbf{R}$ so that for every $\delta > 0$ there is an infinite dimensional subspace Y of H , so that $|a - f(y)| < \delta$, for all $y \in Y$, with $\|y\|=1$. This problem was solved negatively by E. Odell and Th. Schlumprecht (1994).

Operators on Hilbert spaces

Bounded operators

The continuous linear operators $A : H_1 \rightarrow H_2$ from a Hilbert space H_1 to a second Hilbert space H_2 are *bounded* in the sense that they map bounded sets to bounded sets. Conversely, if an operator is bounded, then it is continuous. The space of such bounded linear operators has a norm, the operator norm given by

$$\|A\| = \sup \{ \|Ax\| : \|x\| \leq 1 \}.$$

The sum and the composite of two bounded linear operators is again bounded and linear. For y in H_2 , the map that sends $x \in H_1$ to $\langle Ax, y \rangle$ is linear and continuous, and according to the Riesz representation theorem can therefore be represented in the form

$$\langle x, A^*y \rangle = \langle Ax, y \rangle$$

for some vector A^*y in H_1 . This defines another bounded linear operator $A^* : H_2 \rightarrow H_1$, the adjoint of A . One can see that $A^{**} = A$.

The set $B(H)$ of all bounded linear operators on H , together with the addition and composition operations, the norm and the adjoint operation, is a C^* -algebra, which is a type of operator algebra.

An element A of $B(H)$ is called *self-adjoint* or *Hermitian* if $A^* = A$. If A is Hermitian and $\langle Ax, x \rangle \geq 0$ for every x , then A is called *non-negative*, written $A \geq 0$; if equality holds only when $x = 0$, then A is called *positive*. The set of self adjoint operators admits a partial order, in which $A \geq B$ if $A - B \geq 0$. If A has the form B^*B for some B , then A is non-negative; if B is invertible, then A is positive. A converse is also true in the sense that, for a non-negative operator A , there exists a unique non-negative square root B such that

$$A = B^2 = B^*B.$$

In a sense made precise by the spectral theorem, self-adjoint operators can usefully be thought of as operators that are "real". An element A of $B(H)$ is called *normal* if $A^*A = AA^*$. Normal operators decompose into the sum of a self-adjoint operators and an imaginary multiple of a self adjoint operator

$$A = \frac{A + A^*}{2} + i \frac{(A - A^*)}{2i}$$

that commute with each other. Normal operators can also usefully be thought of in terms of their real and imaginary parts.

An element U of $B(H)$ is called *unitary* if U is invertible and its inverse is given by U^* . This can also be expressed by requiring that U be onto and $\langle Ux, Uy \rangle = \langle x, y \rangle$ for all x and y in H . The unitary operators form a group under composition, which is the isometry group of H .

An element of $B(H)$ is *compact* if it sends bounded sets to relatively compact sets. Equivalently, a bounded operator T is compact if, for any bounded sequence $\{x_k\}$, the sequence $\{Tx_k\}$ has a convergent subsequence. Many integral operators are compact, and in fact define a special class of operators known as Hilbert–Schmidt operators that are especially important in the study of integral equations. Fredholm operators are those which differ from a compact operator by a multiple of the identity, and are equivalently characterized as operators with a finite dimensional kernel and cokernel. The index of a Fredholm operator T is defined by

$$\text{index } T = \dim \ker T - \dim \text{coker } T.$$

The index is homotopy invariant, and plays a deep role in differential geometry via the Atiyah–Singer index theorem.

Unbounded operators

Unbounded operators are also tractable in Hilbert spaces, and have important applications to quantum mechanics.^[54] An unbounded operator T on a Hilbert space H is defined to be a linear operator whose domain $D(T)$ is a linear subspace of H . Often the domain $D(T)$ is a dense subspace of H , in which case T is known as a densely-defined operator.

The adjoint of a densely defined unbounded operator is defined in essentially the same manner as for bounded operators. Self-adjoint unbounded operators play the role of the *observables* in the mathematical formulation of quantum mechanics. Examples of self-adjoint unbounded operators on the Hilbert space $L^2(\mathbf{R})$ are:^[55]

- A suitable extension of the differential operator

$$(Af)(x) = i \frac{d}{dx} f(x),$$

where i is the imaginary unit and f is a differentiable function of compact support.

- The multiplication-by- x operator:

$$(Bf)(x) = xf(x).$$

These correspond to the momentum and position observables, respectively. Note that neither A nor B is defined on all of H , since in the case of A the derivative need not exist, and in the case of B the product function need not be square integrable. In both cases, the set of possible arguments form dense subspaces of $L^2(\mathbf{R})$.

Constructions

Direct sums

Two Hilbert spaces H_1 and H_2 can be combined into another Hilbert space, called the (orthogonal) direct sum,^[56] and denoted

$$H_1 \oplus H_2,$$

consisting of the set of all ordered pairs (x_1, x_2) where $x_i \in H_i$, $i = 1, 2$, and inner product defined by

$$\langle (x_1, x_2), (y_1, y_2) \rangle_{H_1 \oplus H_2} = \langle x_1, y_1 \rangle_{H_1} + \langle x_2, y_2 \rangle_{H_2}.$$

More generally, if H_i is a family of Hilbert spaces indexed by $i \in I$, then the direct sum of the H_i , denoted

$$\bigoplus_{i \in I} H_i$$

consists of the set of all indexed families

$$x = (x_i \in H_i | i \in I) \in \prod_{i \in I} H_i$$

in the Cartesian product of the H_i such that

$$\sum_{i \in I} \|x_i\|^2 < \infty.$$

The inner product is defined by

$$\langle x, y \rangle = \sum_{i \in I} \langle x_i, y_i \rangle_{H_i}.$$

Each of the H_i is included as a closed subspace in the direct sum of all of the H_i . Moreover, the H_i are pairwise orthogonal. Conversely, if there is a system of closed subspaces V_i , $i \in I$, in a Hilbert space H which are pairwise orthogonal and whose union is dense in H , then H is canonically isomorphic to the direct sum of V_i . In this case, H is called the internal direct sum of the V_i . A direct sum (internal or external) is also equipped with a family of orthogonal projections E_i onto the i th direct summand H_i . These projections are bounded, self-adjoint, idempotent operators which satisfy the orthogonality condition

$$E_i E_j = 0, \quad i \neq j.$$

The spectral theorem for compact self-adjoint operators on a Hilbert space H states that H splits into an orthogonal direct sum of the eigenspaces of an operator, and also gives an explicit decomposition of the operator as a sum of projections onto the eigenspaces. The direct sum of Hilbert spaces also appears in quantum mechanics as the Fock space of a system containing a variable number of particles, where each Hilbert space in the direct sum corresponds to an additional degree of freedom for the quantum mechanical system. In representation theory, the Peter-Weyl theorem guarantees that any unitary representation of a compact group on a Hilbert space splits as the direct sum of finite-dimensional representations.

Tensor products

If H_1 and H_2 , then one defines an inner product on the (ordinary) tensor product as follows. On simple tensors, let

$$\langle x_1 \otimes x_2, y_1 \otimes y_2 \rangle = \langle x_1, y_1 \rangle \langle x_2, y_2 \rangle.$$

This formula then extends by sesquilinearity to an inner product on $H_1 \otimes H_2$. The Hilbertian tensor product of H_1 and H_2 , sometimes denoted by $H_1 \widehat{\otimes} H_2$, is the Hilbert space obtained by completing $H_1 \otimes H_2$ for the metric associated to this inner product.^[57]

An example is provided by the Hilbert space $L^2([0, 1])$. The Hilbertian tensor product of two copies of $L^2([0, 1])$ is isometrically and linearly isomorphic to the space $L^2([0, 1]^2)$ of square-integrable functions on the square $[0, 1]^2$. This isomorphism sends a simple tensor $f_1 \otimes f_2$ to the function

$$(s, t) \mapsto f_1(s) f_2(t)$$

on the square.

This example is typical in the following sense.^[58] Associated to every simple tensor product $x_1 \otimes x_2$ is the rank one operator

$$x^* \in H_1^* \rightarrow x^*(x_1) x_2$$

from the (continuous) dual H_1^* to H_2 . This mapping defined on simple tensors extends to a linear identification between $H_1 \otimes H_2$ and the space of finite rank operators from H_1^* to H_2 . This extends to a linear isometry of the Hilbertian tensor product $H_1 \widehat{\otimes} H_2$ with the Hilbert space $HS(H_1^*, H_2)$ of Hilbert-Schmidt operators from H_1^* to H_2 .

Orthonormal bases

The notion of an orthonormal basis from linear algebra generalizes over to the case of Hilbert spaces.^[59] In a Hilbert space H , an orthonormal basis is a family $\{e_k\}_{k \in B}$ of elements of H satisfying the conditions:

1. *Orthogonality*: Every two different elements of B are orthogonal: $\langle e_k, e_j \rangle = 0$ for all k, j in B with $k \neq j$.
2. *Normalization*: Every element of the family has norm 1: $\|e_k\| = 1$ for all k in B .
3. *Completeness*: The linear span of the family $e_k, k \in B$, is dense in H .

A system of vectors satisfying the first two conditions is called an orthonormal system or an orthonormal set (or an orthonormal sequence if B is countable). Such a system is always linearly independent. Completeness of an orthonormal system of vectors of a Hilbert space can be equivalently restated as:

$$\text{if } \langle v, e_k \rangle = 0 \text{ for all } k \in B \text{ and some } v \in H \text{ then } v = 0.$$

This is related to the fact that the only vector orthogonal to a dense linear subspace is the zero vector, for if S is any orthonormal set and v is orthogonal to S , then v is orthogonal to the closure of the linear span of S , which is the whole space.

Examples of orthonormal bases include:

- the set $\{(1,0,0), (0,1,0), (0,0,1)\}$ forms an orthonormal basis of $\mathbf{R}^3$ with the dot product;

- the sequence $\{f_n : n \in \mathbb{Z}\}$ with $f_n(x) = \exp(2\pi i n x)$ forms an orthonormal basis of the complex space $L^2([0,1])$;

In the infinite-dimensional case, an orthonormal basis will not be a basis in the sense of linear algebra; to distinguish the two, the latter basis is also called a Hamel basis. That the span of the basis vectors is dense implies that every vector in the space can be written as the sum of an infinite series, and the orthogonality implies that this decomposition is unique.

Sequence spaces

The space ℓ^2 of square-summable sequences of complex numbers has an orthonormal basis

$$e_1 = (1, 0, 0, \dots)$$

$$e_2 = (0, 1, 0, \dots)$$

$\vdots$

More generally, if B is any set, then one can form a Hilbert space of sequences with index set B , defined by

$$\ell^2(B) = \left\{ x : B \xrightarrow{x} \mathbb{C} \mid \sum_{b \in B} |x(b)|^2 < \infty \right\}.$$

The summation over B is here defined by

$$\sum_{b \in B} |x(b)|^2 = \sup \sum_{n=1}^N |x(b_n)|^2$$

the supremum being taken over all finite subsets of B . It follows that, in order for this sum to be finite, every element of $\ell^2(B)$ has only countably many nonzero terms. This space becomes a Hilbert space with the inner product

$$\langle x, y \rangle = \sum_{b \in B} x(b) \overline{y(b)}$$

for all x and y in $\ell^2(B)$. Here the sum also has only countably many nonzero terms, and is unconditionally convergent by the Cauchy–Schwarz inequality.

An orthonormal basis of $\ell^2(B)$ is indexed by the set B , given by

$$e_b(b') = \begin{cases} 1 & \text{if } b = b' \\ 0 & \text{otherwise.} \end{cases}$$

Bessel's inequality and Parseval's formula

Let $f_1, \dots, f_n$ be a finite orthonormal system in H . For an arbitrary vector x in H , let

$$y = \sum_{j=1}^n \langle x, f_j \rangle f_j.$$

Then $\langle x, f_k \rangle = \langle y, f_k \rangle$ for every $k = 1, \dots, n$. It follows that $x - y$ is orthogonal to each f_k , hence $x - y$ is orthogonal to y . Using the Pythagorean identity twice, it follows that

$$\|x\|^2 = \|x - y\|^2 + \|y\|^2 \geq \|y\|^2 = \sum_{j=1}^n |\langle x, f_j \rangle|^2.$$

Let $\{f_i\}$, $i \in I$, be an arbitrary orthonormal system in H . Applying the preceding inequality to every finite subset J of I gives the *Bessel inequality*^[60]

$$\sum_{i \in I} |\langle x, f_i \rangle|^2 \leq \|x\|^2, \quad x \in H$$

(according to the definition of the sum of an arbitrary family of non-negative real numbers).

Geometrically, Bessel's inequality implies that the orthogonal projection of x onto the linear subspace spanned by the f_i has norm that does not exceed that of x . In two dimensions, this is the assertion that the length of the leg of a right

triangle may not exceed the length of the hypotenuse.

Bessel's inequality is a stepping stone to the more powerful Parseval identity which governs the case when Bessel's inequality is actually an equality. If $\{e_k\}_{k \in B}$ is an orthonormal basis of H , then every element x of H may be written as

$$x = \sum_{k \in B} \langle x, e_k \rangle e_k.$$

Even if B is uncountable, Bessel's inequality guarantees that the expression is well-defined and consists only of countably many nonzero terms. This sum is called the *Fourier expansion* of x , and the individual coefficients $\langle x, e_k \rangle$ are the *Fourier coefficients* of x . Parseval's formula is then

$$\|x\|^2 = \sum_{k \in B} |\langle x, e_k \rangle|^2.$$

Conversely, if $\{e_k\}$ is an orthonormal set such that Parseval's identity holds for every x , then $\{e_k\}$ is an orthonormal basis.

Hilbert dimension

As a consequence of Zorn's lemma, every Hilbert space admits an orthonormal basis; furthermore, any two orthonormal bases of the same space have the same cardinality, called the Hilbert dimension of the space.^[61] For instance, since $\ell^2(B)$ has an orthonormal basis indexed by B , its Hilbert dimension is the cardinality of B (which may be a finite integer, or a countable or uncountable cardinal number).

As a consequence of Parseval's identity, if $\{e_k\}_{k \in B}$ is an orthonormal basis of H , then the map $\Phi : H \rightarrow \ell^2(B)$ defined by $\Phi(x) = (\langle x, e_k \rangle)_{k \in B}$ is an isometric isomorphism of Hilbert spaces: it is a bijective linear mapping such that

$$\langle \Phi(x), \Phi(y) \rangle_{\ell^2(B)} = \langle x, y \rangle_H$$

for all x and y in H . The cardinal number of B is the Hilbert dimension of H . Thus every Hilbert space is isometrically isomorphic to a sequence space $\ell^2(B)$ for some set B .

Separable spaces

A Hilbert space is separable if and only if it admits a countable orthonormal basis. All infinite-dimensional separable Hilbert spaces are therefore isometrically isomorphic to ℓ^2 .

In the past, Hilbert spaces were often required to be separable as part of the definition.^[62] Most spaces used in physics are separable, and since these are all isomorphic to each other, one often refers to any infinite-dimensional separable Hilbert space as "the Hilbert space" or just "Hilbert space".^[63] Even in quantum field theory, most of the Hilbert spaces are in fact separable, as stipulated by the Wightman axioms. However, it is sometimes argued that non-separable Hilbert spaces are also important in quantum field theory, roughly because the systems in the theory possess an infinite number of degrees of freedom and any infinite Hilbert tensor product (of spaces of dimension greater than one) is non-separable.^[64] For instance, a bosonic field can be naturally thought of as an element of a tensor product whose factors represent harmonic oscillators at each point of space. From this perspective, the natural state space of a boson might seem to be a non-separable space.^[64] However, it is only a small separable subspace of the full tensor product that can contain physically meaningful fields (on which the observables can be defined). Another non-separable Hilbert space models the state of an infinite collection of particles in an unbounded region of space. An orthonormal basis of the space is indexed by the density of the particles, a continuous parameter, and since the set of possible densities is uncountable, the basis is not countable.^[64]

Orthogonal complements and projections

If S is a subset of a Hilbert space H , the set of vectors orthogonal to S is defined by

$$S^\perp = \{x \in H : \langle x, s \rangle = 0 \ \forall s \in S\}.$$

$S^\perp$ is a closed subspace of H and so forms itself a Hilbert space. If V is a closed subspace of H , then $V^\perp$ is called the *orthogonal complement* of V . In fact, every x in H can then be written uniquely as $x = v + w$, with v in V and w in $V^\perp$. Therefore, H is the internal Hilbert direct sum of V and $V^\perp$.

The linear operator $P_V : H \rightarrow H$ which maps x to v is called the *orthogonal projection* onto V . There is a natural one-to-one correspondence between the set of all closed subspaces of H and the set of all bounded self-adjoint operators P such that $P^2 = P$. Specifically,

Theorem. The orthogonal projection P_V is a self-adjoint linear operator on H of norm ≤ 1 with the property $P_V^2 = P_V$. Moreover, any self-adjoint linear operator E such that $E^2 = E$ is of the form P_V , where V is the range of E . For every x in H , $P_V(x)$ is the unique element v of V which minimizes the distance $\|x - v\|$.

This provides the geometrical interpretation of $P_V(x)$: it is the best approximation to x by elements of V .^[65]

An operator P such that $P = P^2 = P^*$ is called an orthogonal projection. The orthogonal projection P_V onto a closed subspace V of H is the adjoint of the inclusion mapping

$$i_V : V \rightarrow H,$$

meaning that

$$\langle i_V x, y \rangle = \langle x, P_V y \rangle$$

for all $x \in H$ and $y \in V$. Projections P_U and P_V are called mutually orthogonal if $P_U P_V = 0$. This is equivalent to U and V being orthogonal as subspaces of H . As a result, the sum of the two projections P_U and P_V is only a projection if U and V are orthogonal to each other, and in that case $P_U + P_V = P_{U+V}$. The composite $P_U P_V$ is generally not a projection; in fact, the composite is a projection if and only if the two projections commute, and in that case $P_U P_V = P_{U \cap V}$.

The operator norm of a projection P onto a non-zero closed subspace is equal to one:

$$\|P\| = \sup_{x \in H, x \neq 0} \frac{\|Px\|}{\|x\|} = 1.$$

Every closed subspace V of a Hilbert space is therefore the image of an operator P of norm one such that $P^2 = P$. In fact this property characterizes Hilbert spaces.^[66]

- A Banach space of dimension higher than 2 is (isometrically) a Hilbert space if and only if, to every closed subspace V , there is an operator P_V of norm one whose image is V such that $P_V^2 = P_V$.

While this result characterizes the metric structure of a Hilbert space, the structure of a Hilbert space as a topological vector space can itself be characterized in terms of the presence of complementary subspaces.^[67]

- A Banach space X is topologically and linearly isomorphic to a Hilbert space if and only if, to every closed subspace V , there is a closed subspace W such that X is equal to the internal direct sum $V \oplus W$.

The orthogonal complement satisfies some more elementary results. It is a monotone function in the sense that if $U \subset V$, then $V^\perp \subseteq U^\perp$ with equality holding if and only if V is contained in the closure of U . This result is a special case of the Hahn–Banach theorem. The closure of a subspace can be completely characterized in terms of the orthogonal complement: If V is a subspace of H , then the closure of V is equal to $V^{\perp\perp}$. The orthogonal complement is thus a Galois connection on the partial order of subspaces of a Hilbert space. In general, the orthogonal complement of a sum of subspaces is the intersection of the orthogonal complements.^[68] $(\sum_i V_i)^\perp = \bigcap_i V_i^\perp$. If the V_i are in addition closed, then $\overline{\sum_i V_i} = (\bigcap_i V_i)^\perp$.

Spectral theory

There is a well-developed spectral theory for self-adjoint operators in a Hilbert space, that is roughly analogous to the study of symmetric matrices over the reals or self-adjoint matrices over the complex numbers.^[69] In the same sense, one can obtain a "diagonalization" of a self-adjoint operator as a suitable sum (actually an integral) of orthogonal projection operators.

The spectrum of an operator T , denoted $\sigma(T)$ is the set of complex numbers λ such that $T - \lambda$ lacks a continuous inverse. If T is bounded, then the spectrum is always a compact set in the complex plane, and lies inside the disc $|z| \leq \|T\|$. If T is self-adjoint, then the spectrum is real. In fact, it is contained in the interval $[m, M]$ where

$$m = \inf_{\|x\|=1} \langle Tx, x \rangle, \quad M = \sup_{\|x\|=1} \langle Tx, x \rangle.$$

Moreover, m and M are both actually contained within the spectrum.

The eigenspaces of an operator T are given by

$$H_\lambda = \ker(T - \lambda).$$

Unlike with finite matrices, not every element of the spectrum of T must be an eigenvalue: the linear operator $T - \lambda$ may only lack an inverse because it is not surjective. Elements of the spectrum of an operator in the general sense are known as *spectral values*. Since spectral values need not be eigenvalues, the spectral decomposition is often more subtle than in finite dimensions.

However, the spectral theorem of a self-adjoint operator T takes a particularly simple form if, in addition, T is assumed to be a compact operator. The spectral theorem for compact self-adjoint operators states:^[70]

- A compact self-adjoint operator T has only countably (or finitely) many spectral values. The spectrum of T has no limit point in the complex plane except possibly zero. The eigenspaces of T decompose H into an orthogonal direct sum:

$$H = \bigoplus_{\lambda \in \sigma(T)} H_\lambda.$$

Moreover, if E_λ denotes the orthogonal projection onto the eigenspace H_λ , then

$$T = \sum_{\lambda \in \sigma(T)} \lambda E_\lambda$$

where the sum converges with respect to the norm on $B(H)$.

This theorem plays a fundamental role in the theory of integral equations, as many integral operators are compact, in particular those that arise from Hilbert-Schmidt operators.

The general spectral theorem for self-adjoint operators involves a kind of operator-valued Riemann–Stieltjes integral, rather than an infinite summation.^[71] The *spectral family* associated to T associates to each real number λ an operator E_λ , which is the projection onto the nullspace of the operator $(T - \lambda)^+$, where the positive part of a self-adjoint operator is defined by

$$A^+ = \frac{1}{2} (\sqrt{A^2} + A).$$

The operators E_λ are monotone increasing relative to the partial order defined on self-adjoint operators; the eigenvalues correspond precisely to the jump discontinuities. One has the spectral theorem, which asserts

$$T = \int_{\mathbb{R}} \lambda dE_\lambda.$$

The integral is understood as a Riemann–Stieltjes integral, convergent with respect to the norm on $B(H)$. In particular, one has the ordinary scalar-valued integral representation

$$\langle Tx, y \rangle = \int_{\mathbb{R}} \lambda d\langle E_\lambda x, y \rangle.$$

A somewhat similar spectral decomposition holds for normal operators, although because the spectrum may now contain non-real complex numbers, the operator-valued Stieltjes measure dE_λ must instead be replaced by a resolution of the identity.

A major application of spectral methods is the spectral mapping theorem, which allows one to apply to a self-adjoint operator T any continuous complex function f defined on the spectrum of T by forming the integral

$$f(T) = \int_{\sigma(T)} f(\lambda) dE_\lambda.$$

The resulting continuous functional calculus has applications in particular to pseudodifferential operators.^[72]

The spectral theory of *unbounded* self-adjoint operators is only marginally more difficult than for bounded operators. The spectrum of an unbounded operator is defined in precisely the same way as for bounded operators: λ is a spectral value if the resolvent operator

$$R_\lambda = (T - \lambda)^{-1}$$

fails to be a well-defined continuous operator. The self-adjointness of T still guarantees that the spectrum is real. Thus the essential idea of working with unbounded operators is to look instead at the resolvent R_λ where λ is non-real. This is a *bounded* normal operator, which admits a spectral representation that can then be transferred to a spectral representation of T itself. A similar strategy is used, for instance, to study the spectrum of the Laplace operator: rather than address the operator directly, one instead looks at an associated resolvent such as a Riesz potential or Bessel potential.

A precise version of the spectral theorem which holds in this case is:^[73]

Given a densely-defined self-adjoint operator T on a Hilbert space H , there corresponds a unique resolution of the identity E on the Borel sets of $\mathbf{R}$, such that

$$\langle Tx, y \rangle = \int_{\mathbf{R}} \lambda dE_{x,y}(\lambda)$$

for all $x \in D(T)$ and $y \in H$. The spectral measure E is concentrated on the spectrum of T .

There is also a version of the spectral theorem that applies to unbounded normal operators.

Notes

- [1] Marsden 1974, §2.8
- [2] The mathematical material in this section can be found in any good textbook on functional analysis, such as Dieudonné (1960), Hewitt & Stromberg (1965), Reed & Simon (1980) or Rudin (1980).
- [3] In some conventions, inner products are linear in their second arguments instead.
- [4] Dieudonné 1960, §6.2
- [5] Dieudonné 1960
- [6] Largely from the work of Hermann Grassmann, at the urging of August Ferdinand Möbius (Boyer & Merzbach 1991, pp. 584–586). The first modern axiomatic account of abstract vector spaces ultimately appeared in Giuseppe Peano's 1888 account (Grattan-Guinness 2000, §5.2.2; O'Connor & Robertson 1996).
- [7] A detailed account of the history of Hilbert spaces can be found in Bourbaki 1987.
- [8] Schmidt 1908
- [9] Titchmarsh 1946, §IX.1
- [10] Lebesgue 1904. Further details on the history of integration theory can be found in Bourbaki (1987) and Saks (2005).
- [11] Bourbaki 1987.
- [12] Dunford & Schwartz 1958, §IV.16
- [13] In Dunford & Schwartz (1958, §IV.16), the result that every linear functional on $L^2[0,1]$ is represented by integration is jointly attributed to Fréchet (1907) and Riesz (1907). The general result, that the dual of a Hilbert space is identified with the Hilbert space itself, can be found in Riesz (1934).
- [14] von Neumann 1929.
- [15] Kline 1972, p. 1092
- [16] Hilbert, Nordheim & von Neumann 1927.
- [17] Weyl 1931.

- [18] Prugovečki 1981, pp. 1–10.
- [19] von Neumann 1932
- [20] Halmos 1957, Section 42.
- [21] Hewitt & Stromberg 1965.
- [22] Bers, John & Schechter 1981.
- [23] Giusti 2003.
- [24] Stein 1970
- [25] Details can be found in Warner (1983).
- [26] A general reference on Hardy spaces is the book Duren (1970).
- [27] Krantz 2002, §1.4
- [28] Krantz 2002, §1.5
- [29] Young 1987, Chapter 9.
- [30] The eigenvalues of the Fredholm kernel are $1/\lambda$, which tend to zero.
- [31] More detail on finite element methods from this point of view can be found in Brenner & Scott (2005).
- [32] Reed & Simon 1980
- [33] A treatment of Fourier series from this point of view is available, for instance, in Rudin (1987) or Folland (2009).
- [34] Halmos 1957, §5
- [35] Bachman, Narici & Beckenstein 2000
- [36] Stein & Weiss 1971, §IV.2.
- [37] Lancos 1988, pp. 212–213
- [38] Lanczos 1988, Equation 4-3.10
- [39] The classic reference for spectral methods is Courant & Hilbert 1953. A more up-to-date account is Reed & Simon 1975.
- [40] Kac 1966
- [41] Dirac 1930
- [42] von Neumann 1955
- [43] Young 1988, p. 23.
- [44] Clarkson 1936.
- [45] Rudin 1987, Theorem 4.10
- [46] Dunford & Schwartz 1958, II.4.29
- [47] Rudin 1987, Theorem 4.11
- [48] Weidmann 1980, Theorem 4.8
- [49] Weidmann 1980, §4.5
- [50] Buttazzo, Giaquinta & Hildebrandt 1998, Theorem 5.17
- [51] Halmos 1982, Problem 52, 58
- [52] Rudin 1973
- [53] Trèves 1967, Chapter 18
- [54] See Prugovečki (1981), Reed & Simon (1980, Chapter VIII) and Folland (1989).
- [55] Prugovečki 1981, III, §1.4
- [56] Dunford & Schwartz 1958, IV.4.17-18
- [57] Weidmann 1980, §3.4
- [58] Kadison & Ringrose 1983, Theorem 2.6.4
- [59] Dunford & Schwartz 1958, §IV.4.
- [60] For the case of finite index sets, see, for instance, Halmos 1957, §5. For infinite index sets, see Weidmann 1980, Theorem 3.6.
- [61] Levitan 2001. Many authors, such as Dunford & Schwartz (1958, §IV.4), refer to this just as the dimension. Unless the Hilbert space is finite dimensional, this is not the same thing as its dimension as a linear space (the cardinality of a Hamel basis).
- [62] Prugovečki 1981, I, §4.2
- [63] von Neumann (1955) defines a Hilbert space via a countable Hilbert basis, which amounts to an isometric isomorphism with ℓ^2 . The convention still persists in most rigorous treatments of quantum mechanics; see for instance Sobrino 1996, Appendix B.
- [64] Streater & Wightman 1964, pp. 86–87
- [65] Young 1988, Theorem 15.3
- [66] Kakutani 1939
- [67] Lindenstrauss & Tzafriri 1971
- [68] Halmos 1957, §12
- [69] A general account of spectral theory in Hilbert spaces can be found in Riesz & Sz Nagy (1990). A more sophisticated account in the language of C^* -algebras is in Rudin (1973) or Kadison & Ringrose (1997)
- [70] See, for instance, Riesz & Sz Nagy (1990, Chapter VI) or Weidmann 1980, Chapter 7. This result was already known to Schmidt (1907) in the case of operators arising from integral kernels.
- [71] Riesz & Sz Nagy 1990, §§107–108
- [72] Shubin 1987

[73] Rudin 1973, Theorem 13.30.

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External links

- Hilbert Space at Mathworld (<http://mathworld.wolfram.com/HilbertSpace.html>)
 - 245B, notes 5: Hilbert spaces (<http://terrytao.wordpress.com/2009/01/17/254a-notes-5-hilbert-spaces/>) by Terence Tao
-

Operator algebra

In functional analysis, an **operator algebra** is an algebra of continuous linear operators on a topological vector space with the multiplication given by the composition of mappings. Although it is usually classified as a branch of functional analysis, it has direct applications to representation theory, differential geometry, quantum statistical mechanics and quantum field theory.

Such algebras can be used to study arbitrary sets of operators with little algebraic relation *simultaneously*. From this point of view, operator algebras can be regarded as a generalization of spectral theory of a single operator. In general operator algebras are non-commutative rings.

An operator algebra is typically required to be closed in a specified operator topology inside the algebra of the whole continuous linear operators. In particular, it is a set of operators with both algebraic and topological closure properties. In some disciplines such properties are axiomized and algebras with certain topological structure become the subject of the research.

Though algebras of operators are studied in various contexts (for example, algebras of pseudo-differential operators acting on spaces of distributions), the term *operator algebra* is usually used in reference to algebras of bounded operators on a Banach space or, even more specially in reference to algebras of operators on a separable Hilbert space, endowed with the operator norm topology.

In the case of operators on a Hilbert space, the adjoint map on operators gives a natural involution which provides an additional algebraic structure which can be imposed on the algebra. In this context, the best studied examples are self-adjoint operator algebras, meaning that they are closed under taking adjoints. These include C^* -algebras and von Neumann algebras. C^* -algebras can be easily characterized abstractly by a condition relating the norm, involution and multiplication. Such abstractly defined C^* -algebras can be identified to a certain closed subalgebra of the algebra of the continuous linear operators on a suitable Hilbert space. A similar result holds for von Neumann algebras.

Commutative self-adjoint operator algebras can be regarded as the algebra of complex valued continuous functions on a locally compact space, or that of measurable functions on a standard measurable space. Thus, general operator algebras are often regarded as a noncommutative generalizations of these algebras, or the structure of the *base space* on which the functions are defined. This point of view is elaborated as the philosophy of noncommutative geometry, which tries to study various non-classical and/or pathological objects by noncommutative operator algebras.

Examples of operator algebras which are not self-adjoint include:

- nest algebras
- many commutative subspace lattice algebras
- many limit algebras

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Quantum algebra

Quantum algebra is one of the top-level mathematics categories used by the arXiv.

Subjects include:

- Quantum groups
- Skein theories
- Operadic algebra
- Diagrammatic algebra
- Quantum field theory

External links

- Quantum algebra at arxiv.org ^[1]

References

[1] <http://arxiv.org/list/math.QA/current>

Local quantum field theory

The **Haag-Kastler** axiomatic framework for quantum field theory, named after Rudolf Haag and Daniel Kastler, is an application to *local* quantum physics of C^* -algebra theory. It is therefore also known as **Algebraic Quantum Field Theory (AQFT)**. The axioms are stated in terms of an algebra given for every open set in Minkowski space, and mappings between those.

Let **Mink** be the category of open subsets of Minkowski space M with inclusion maps as morphisms. We are given a covariant functor $\mathcal{A}$ from **Mink** to **uC*alg**, the category of unital C^* algebras, such that every morphism in **Mink** maps to a monomorphism in **uC*alg** (*isotony*).

The Poincaré group acts continuously on **Mink**. There exists a pullback of this action, which is continuous in the norm topology of $\mathcal{A}(M)$ (Poincaré covariance).

Minkowski space has a causal structure. If an open set V lies in the causal complement of an open set U , then the image of the maps

$$\mathcal{A}(i_{U,U \cup V})$$

and

$$\mathcal{A}(i_{V,U \cup V})$$

commute (spacelike commutativity). If $\bar{U}$ is the causal completion of an open set U , then $\mathcal{A}(i_{U,\bar{U}})$ is an isomorphism (primitive causality).

A state with respect to a C^* -algebra is a positive linear functional over it with unit norm. If we have a state over $\mathcal{A}(M)$, we can take the "partial trace" to get states associated with $\mathcal{A}(U)$ for each open set via the net monomorphism. It's easy to show the states over the open sets form a presheaf structure.

According to the GNS construction, for each state, we can associate a Hilbert space representation of $\mathcal{A}(M)$. Pure states correspond to irreducible representations and mixed states correspond to reducible representations. Each irreducible (up to equivalence) is called a superselection sector. We assume there is a pure state called the vacuum such that the Hilbert space associated with it is a unitary representation of the Poincaré group compatible with the Poincaré covariance of the net such that if we look at the Poincaré algebra, the spectrum with respect to energy-momentum (corresponding to spacetime translations) lies on and in the positive light cone. This is the

vacuum sector.

Suggested reading

- Haag, Rudolf (1992). *Local Quantum Physics: Fields, Particles, Algebras*. Springer.

External links

- Local Quantum Physics Crossroads ^[1] - A network of scientists working on Local Quantum Physics
- Algebraic Quantum Field Theory ^[2] - AQFT resources at the University of Hamburg

Topological order

In physics, **topological order** ^[1] is a new kind of order (a new kind of organization of particles) in a quantum state that is beyond the Landau symmetry-breaking description. It cannot be described by local order parameters and long range correlations. However, topological orders can be described by a new set of quantum numbers, such as ground state degeneracy, quasiparticle fractional statistics, edge states, topological entropy, etc. Roughly speaking, topological order is a pattern of long-range quantum entanglement in quantum states. States with different topological orders can change into each other only through a phase transition.

Background

Although all matter is formed by atoms, matter can have very different properties and appear in very different forms, such as solid, liquid, superfluid, magnet, etc. According to condensed matter physics and the principle of emergence, the different properties of materials originate from the different ways in which the atoms are organized in the materials. Those different organizations of the atoms (or other particles) are formally called the orders in the materials.

Atoms can organize in many ways which lead to many different orders and many different types of materials. Landau symmetry-breaking theory provides a general understanding of these different orders. It points out that different orders really correspond to different symmetries in the organizations of the constituent atoms. As a material changes from one order to another order (i.e., as the material undergoes a phase transition), what happens is that the symmetry of the organization of the atoms changes.

For example, atoms have a random distribution in a liquid, so a liquid remains the same as we displace it by an arbitrary distance. We say that a liquid has a *continuous translation symmetry*. After a phase transition, a liquid can turn into a crystal. In a crystal, atoms organize into a regular array (a lattice). A lattice remains unchanged only when we displace it by a particular distance (integer times of lattice constant), so a crystal has only *discrete translation symmetry*. The phase transition between a liquid and a crystal is a transition that reduces the continuous translation symmetry of the liquid to the discrete symmetry of the crystal. Such change in symmetry is called *symmetry breaking*. The essence of the difference between liquids and crystals is therefore that the organizations of atoms have different symmetries in the two phases.

Landau symmetry-breaking theory is a very successful theory. For a long time, physicists believed that Landau symmetry-breaking theory describes all possible orders in materials, and all possible (continuous) phase transitions.

The discovery and characterization of topological order

However, since late 1980s, it has become gradually apparent that Landau symmetry-breaking theory may not describe all possible orders. In an attempt to explain high temperature superconductivity^[2] people introduced chiral spin state.^{[3] [4]} At first, physicists still wanted to use Landau symmetry-breaking theory to describe the chiral spin state. They identified the chiral spin state as a state that breaks the time reversal and parity symmetries, but not the spin rotation symmetry. This should be the end of story according to Landau's symmetry breaking description of orders. However, it was quickly realized that there are many different chiral spin states that have exactly the same symmetry, so symmetry alone was not enough to characterize different chiral spin states. This means that the chiral spin states contain a new kind of order that is beyond the usual symmetry description^[5]. The proposed, new kind of order was named "topological order"^[6]. (The name "topological order" is motivated by the low energy effective theory of the chiral spin states which is a topological quantum field theory (TQFT)^{[7] [8] [9]}). New quantum numbers, such as ground state degeneracy^[10] and the non-Abelian Berry's phase of degenerate ground states^[11], were introduced to characterize the different topological orders in chiral spin states. Recently, it was shown that topological orders can also be characterized by topological entropy^{[12] [13]}.

But experiments soon indicated that chiral spin states do not describe high-temperature superconductors, and the theory of topological order became a theory with no experimental realization. However, the similarity between chiral spin states and quantum Hall states allows one to use the theory of topological order to describe different quantum Hall states.^[14] Just like chiral spin states, different quantum Hall states all have the same symmetry and are beyond the Landau symmetry-breaking description. One finds that the different orders in different quantum Hall states can indeed be described by topological orders, so the topological order does have experimental realizations.

Fractional quantum Hall (FQH) states were discovered in 1982^{[15] [16]} before the introduction of the concept of topological order. But FQH states are not the first experimentally discovered topologically ordered states. Superconductors discovered in 1911 are the first, which have a $\mathbb{Z}_2$ topological order (note, however, that superconductivity does fall within the Ginzburg-Landau theory description of phase transitions - in fact the prediction of the vortex state in superconductors was one of the main successes of Ginzburg-Landau theory).^{[17] [18]}

Mechanism of topological order

A large class of topological orders is realized through a mechanism called string-net condensation^[19]. This class of topological orders can be classified by utilizing tensor category (or monoidal category) theory. One finds that string-net condensation can generate infinitely many different types of topological orders, which may indicate that there are many different new types of materials remaining to be discovered.

The collective motions of condensed strings give rise to excitations above the string-net condensed states. Those excitations turn out to be gauge bosons. The ends of strings are defects which correspond to another type of excitations. Those excitations are the gauge charges and can carry Fermi or fractional statistics.^[20]

The condensations of other extended objects such as "membranes",^[21] "brane-nets",^[22] and fractals also lead to topologically ordered phases^[23] and "quantum glassiness"^[24]

Mathematical foundation of topological order

We know that group theory is the mathematical foundation of symmetry breaking orders. What is the mathematical foundation of topological order? The string-net condensation suggests that tensor category (or monoidal category) theory may be the mathematical foundation of topological order. Quantum operator algebra is a very important mathematical tool in studying topological orders. Some also suggest that topological order is mathematically described by *extended* quantum symmetry^[25].

Applications

The materials described by Landau symmetry-breaking theory have had a substantial impact on technology. For example, Ferromagnetic materials that break spin rotation symmetry can be used as the media of digital information storage. A hard drive made of ferromagnetic materials can store gigabytes of information. Liquid crystals that break the rotational symmetry of molecules find wide application in display technology; nowadays one can hardly find a household without a liquid crystal display somewhere in it. Crystals that break translation symmetry lead to well defined electronic bands which in turn allow us to make semiconducting devices such as transistors.

Different types of Topologically orders are even richer than different types of symmetry-breaking orders. This suggests their potential for exciting, novel applications.

One theorized application would be to use topologically ordered states as media for quantum computing in a technique known as topological quantum computing. A topologically ordered state is a state with complicated non-local quantum entanglement. The non-locality means that the quantum entanglement in a topologically ordered state is distributed among many different particles. As a result, the pattern of quantum entanglements cannot be destroyed by local perturbations. This significantly reduces the effect of decoherence. This suggests that if we use different quantum entanglements in a topologically ordered state to encode quantum information, the information may last much longer.^[26] The quantum information encoded by the topological quantum entanglements can also be manipulated by dragging the topological defects around each other. This process may provide a physical apparatus for performing quantum computations.^[27] Therefore, topologically ordered states may provide natural media for both quantum memory and quantum computation. Such realizations of quantum memory and quantum computation may potentially be made fault tolerant.^[28]

Topologically ordered states in general have a special property that they contain non-trivial boundary states. In many cases, those boundary states become perfect conducting channel that can conduct electricity without generating heat.^[29] This can be another potential application of topological order in electronic devices. For example, the topological insulator^{[30] [31]} is a simple example of topological order. The boundary states of topological insulator play a key role in the detection and the application of topological insulators.

Potential impact

Why is topological order important? Landau symmetry-breaking theory is a cornerstone of condensed matter physics. It is used to define the territory of condensed matter research. The existence of topological order appears to indicate that nature is much richer than Landau symmetry-breaking theory has so far indicated. The exciting time of condensed matter physics is still ahead of us. Some suggest that topological order (or more precisely, string-net condensation) and the local bosonic (spin) models have the potential to provide a unified origin^[32] for photons, electrons and other elementary particles in our universe.^[33]

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Goldstone theorem

In particle and condensed matter physics, **Goldstone bosons** (also known as **Nambu-Goldstone bosons**) are bosons that appear necessarily in models exhibiting spontaneous breakdown of continuous symmetries (cf. spontaneously broken symmetry). They were discovered by Nambu in the context of the BCS superconductivity mechanism,^[1] and subsequently elucidated by Goldstone,^[2] and systematically generalized in the context of quantum field theory.^[3]

These spinless bosons correspond to the spontaneously broken internal symmetry generators, and are characterized by the quantum numbers of these. They transform **nonlinearly** (shift) under the action of these generators, and can thus be excited out of the asymmetric vacuum by these generators. Thus, they can be thought of as the excitations of the field in the broken symmetry directions in group space—and are massless if the spontaneously broken symmetry is *not also broken explicitly*. If, instead, the symmetry is not exact, i.e., if it is *explicitly broken as well as spontaneously broken*, then the Nambu-Goldstone bosons are not massless, though they typically remain relatively light; they are then called **pseudo-Goldstone bosons** or **pseudo-Nambu-Goldstone bosons** (abbreviated *PNGBs*).

Goldstone's theorem

Goldstone's theorem examines a generic continuous symmetry which is spontaneously broken; i.e., its currents are conserved, but the ground state (vacuum) is not invariant under the action of the corresponding charges. Then, necessarily, new massless (or light, if the symmetry is not exact) scalar particles appear in the spectrum of possible excitations. There is one scalar particle—called a Nambu-Goldstone boson—for each generator of the symmetry that is broken; i.e., that does not preserve the ground state. The Nambu-Goldstone mode is a long-wavelength fluctuation of the corresponding order parameter.

There is an arguable loophole in the theorem. If one reads the theorem carefully, it only states that there exist non-vacuum states with arbitrarily small energies. Take for example a chiral $N = 1$ super QCD model with a nonzero squark VEV which is conformal in the IR. The chiral symmetry is a global symmetry which is (partially) spontaneously broken. Some of the "Goldstone bosons" associated with this spontaneous symmetry breaking are charged under the unbroken gauge group and hence, these composite bosons have a continuous mass spectrum with arbitrarily small masses but yet there is no Goldstone boson with exactly zero mass. In other words, the Goldstone bosons are infraparticles.

In theories with gauge symmetry, the Goldstone bosons are "eaten" by the gauge bosons. The latter become massive and their new, longitudinal polarization is provided by the Goldstone boson.

A simple example

Consider a complex scalar field ϕ (phi), with the constraint that $\phi^* \phi = k^2$. One way to get a constraint of this sort is by including a potential

$$\lambda^2 (\phi^* \phi - k^2)^2,$$

and taking the limit as $\lambda \rightarrow \infty$ (this is called the Abelian nonlinear σ -model).

The constraint, and the action, below, are invariant under a $U(1)$ phase transformation, $\delta\phi = i\varepsilon\phi$. The field can be redefined to give a real scalar field (i.e., a spin-zero particle) θ without any constraint by

$$\phi = ke^{i\theta}$$

where θ is the Nambu-Goldstone boson (actually $k\theta$ is), and the $U(1)$ symmetry transformation effects a *shift* on θ , namely $\delta\theta = \varepsilon$, but does not preserve the ground state $|0\rangle$, (i.e. the above infinitesimal transformation *does not*

annihilate it—the hallmark of invariance), as evident in the charge of the current below. The vacuum is degenerate and noninvariant under the spontaneously broken symmetry.

The corresponding Lagrangian density is given by

$$\mathcal{L} = -\frac{1}{2}(\partial^\mu \phi^*)\partial_\mu \phi + m^2 \phi^* \phi = -\frac{1}{2}(-ike^{-i\theta}\partial^\mu \theta)(ike^{i\theta}\partial_\mu \theta) + m^2 k^2 = -\frac{k^2}{2}(\partial^\mu \theta)(\partial_\mu \theta) + m^2 k^2,$$

and the symmetry-induced conserved $U(1)$ current is $J_\mu = -k^2 \partial_\mu \theta$. The charge resulting from this current, Q , shifts θ and the ground state to a new, degenerate, ground state. Thus, a vacuum with $\langle \theta \rangle = 0$ will shift to a *different* vacuum with $\langle \theta \rangle = -\varepsilon$. The current connects the original vacuum with the Nambu-Goldstone state, $\langle 0 | J_0(0) | \theta \rangle \neq 0$.

Note that the constant term $m^2 k^2$ in the Lagrangian density has no physical significance, and the other term in it is simply the kinetic term for a massless scalar.

In general, in a theory with several scalar fields, ϕ_j , the Nambu-Goldstone mode ϕ_g is massless, and parameterises the curve of possible (degenerate) vacuum states. Its hallmark under the broken symmetry transformation is **nonvanishing vacuum expectation** $\langle \delta \phi_g \rangle$, an order parameter, for vanishing $\langle \phi_g \rangle = 0$, at some ground state $|0\rangle$ chosen at the minimum of the potential, $\langle \partial V / \partial \phi_i \rangle = 0$.

This nonvanishing vacuum expectation of the transformation increment, $\langle \delta \phi_g \rangle$, specifies the relevant (Goldstone) *null eigenvector of the mass matrix*, $\langle \partial^2 V / \partial \phi_i \partial \phi_j \rangle \langle \delta \phi_j \rangle = 0$, and hence the corresponding zero-mass eigenvalue.

Goldstone's Argument

The principle behind Goldstone's argument is that the ground state is not unique. Normally, by current conservation, the charge operator for any symmetry current is time-independent,

$$\frac{d}{dt}Q = \frac{d}{dt} \int_x J^0(x) = 0.$$

Acting with the charge operator on the vacuum either *annihilates the vacuum*, if that is symmetric; else, if *not*, as is the case in spontaneous symmetry breaking, it produces a zero-frequency state out of it, through its shift transformation feature illustrated above. (Actually, here, the charge itself is ill-defined; but its better behaved commutators with fields, so, then, the transformation shifts, are still time-invariant, $d\langle \delta \phi_g \rangle / dt = 0$.)

So, if the vacuum is not invariant under the symmetry, action of the charge operator produces a state which is different from the vacuum chosen, but which has zero frequency. This is a long-wavelength oscillation of a field which is nearly stationary: there are states with zero frequency, so that the theory cannot have a mass gap.

This argument is clarified by taking the limit carefully. If an approximate charge operator is applied to the vacuum,

$$\frac{d}{dt}Q_A = \frac{d}{dt} \int_x e^{\frac{-x^2}{2A^2}} J^0(x) = - \int_x e^{\frac{-x^2}{2A^2}} \nabla \cdot J = \int_x \nabla(e^{\frac{-x^2}{2A^2}}) \cdot J,$$

a state with approximately vanishing time derivative is produced,

$$\left\| \frac{d}{dt}Q_A |0\rangle \right\| \approx \frac{1}{A} \|Q_A |0\rangle\|.$$

Assuming a mass gap m_0 , the frequency of any state like the above, which is orthogonal to the vacuum, is at least m_0 ,

$$\left\| \frac{d}{dt}|\psi\rangle \right\| = \|H|\psi\rangle\| \geq m_0 \| |\psi\rangle \|.$$

Letting A become large leads to a contradiction.

This argument fails, however, when the symmetry is gauged, because then the symmetry generator is only performing a gauge transformation. A gauge transformed state is the same exact state, so that acting with a symmetry generator does not get one out of the vacuum.

Nonrelativistic theories

A version of Goldstone's theorem also applies to nonrelativistic theories (and also relativistic theories with spontaneously broken spacetime symmetries, such as Lorentz symmetry or conformal symmetry, rotational, or translational invariance).

It essentially states that, for each spontaneously broken symmetry, there corresponds some quasiparticle with no energy gap—the nonrelativistic version of the mass gap. (Note that the energy here is really $H - \mu N - \vec{\alpha} \cdot \vec{P}$ and not H .) However, two *different* spontaneously broken generators may now give rise to the *same* Nambu-Goldstone boson. For example, in a superfluid, both the U(1) particle number symmetry and Galilean symmetry are spontaneously broken. However, the phonon is the Goldstone boson for both.

In general, the phonon is effectively the Nambu-Goldstone boson for spontaneously broken Galilean/Lorentz symmetry. However, in contrast to the case of internal symmetry breaking, when spacetime symmetries are broken, the order parameter *need not* be a scalar field, but may be a tensor field, and the corresponding independent massless modes may now be *fewer* than the number of spontaneously broken generators, because the Goldstone modes may now be linearly dependent among themselves: e.g., the Goldstone modes for some generators might be expressed as gradients of Goldstone modes for other broken generators.

Nambu-Goldstone fermions

Spontaneously broken global fermionic symmetries, which occur in some supersymmetric models, lead to Nambu-Goldstone fermions, or *goldstinos*.^{[4] [5]} These have spin $\frac{1}{2}$, instead of 0, and carry all quantum numbers of the respective supersymmetry generators broken spontaneously.

(Vestigial bosonic superpartners of these goldstinos under supersymmetries, called *sgoldstinos*, might sometimes also appear. Strictly speaking, however, spontaneous symmetry, and supersymmetry, breaking smashes up ("reduces") multiplet and supermultiplet structures, into the characteristic nonlinear realizations of broken supersymmetry, so that, in a technical sense, goldstinos are superpartners of *all* particles in the theory, of *any spin*.)

Goldstone bosons in nature

- In fluids, the phonon is longitudinal and it is the Goldstone boson of the spontaneously broken Galilean symmetry. In solids, the situation is more complicated; the Goldstone bosons are the longitudinal and transverse phonons and they happen to be the Goldstone bosons of spontaneously broken Galilean, translational, and rotational symmetry with no simple one-to-one correspondence between the Goldstone modes and the broken symmetries.
- In magnets, the original rotational symmetry (present in the absence of an external magnetic field) is spontaneously broken such that the magnetization points into a specific direction. The Goldstone bosons then are the *magnons*, i.e., spin waves in which the local magnetization direction oscillates.
- The *pions* are the pseudo-Goldstone bosons that result from the spontaneous breakdown of the chiral-flavor symmetries of QCD effected by quark condensation due to the strong interaction. These symmetries are further explicitly broken by the masses of the quarks, so that the pions are not massless, but their mass is *significantly smaller* than typical hadron masses.
- The longitudinal polarization components of the W and Z bosons correspond to the Goldstone bosons of the spontaneously broken part of the electroweak symmetry $SU(2) \otimes U(1)$. Because this symmetry is gauged, the three would-be Goldstone bosons are "eaten" by the three gauge bosons corresponding to the three broken generators; this gives these three gauge bosons a mass, and the associated necessary third polarization degree of freedom. This is described in the Standard Model through the Higgs mechanism.

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Algebraic logic

In mathematical logic, **algebraic logic** is the study of logic presented in an algebraic style.

Algebras as models of logics

Algebraic logic treats algebraic structures, often bounded lattices, as models (interpretations) of certain logics, making logic a branch of order theory.

In algebraic logic:

- Variables are tacitly universally quantified over some universe of discourse. There are no existentially quantified variables or open formulas;
- Terms are built up from variables using primitive and defined operations. There are no connectives;
- Formulas, built from terms in the usual way, can be equated if they are logically equivalent. To express a tautology, equate a formula with a truth value;
- The rules of proof are the substitution of equals for equals, and uniform replacement. Modus ponens remains valid, but is seldom employed.

In the table below, the left column contains one or more logical or mathematical systems, and the algebraic structure which are its models are shown on the right in the same row. Some of these structures are either Boolean algebras or proper extensions thereof. Modal and other nonclassical logics are typically modeled by what are called "Boolean algebras with operators."

Algebraic formalisms going beyond first-order logic in at least some respects include:

- Combinatory logic, having the expressive power of set theory;
- Relation algebra, arguably the paradigmatic algebraic logic, can express Peano arithmetic and most axiomatic set theories, including the canonical ZFC.

logical system	its models
Classical sentential logic	Lindenbaum-Tarski algebra Two-element Boolean algebra
Intuitionistic propositional logic	Heyting algebra
Łukasiewicz logic	MV-algebra
Modal logic K	Modal algebra
Lewis's S4	Interior algebra
Lewis's S5; Monadic predicate logic	Monadic Boolean algebra
First-order logic	Cylindric algebra Polyadic algebra Predicate functor logic
Set theory	Combinatory logic Relation algebra

History

On the history of algebraic logic before World War II, see Brady (2000) and Grattan-Guinness (2000) and their ample references. On the postwar history, see Maddux (1991) and Quine (1976).

Algebraic logic has at least two meanings:

- The study of Boolean algebra, begun by George Boole, and of relation algebra, begun by Augustus DeMorgan, extended by Charles Sanders Peirce, and taking definitive form in the work of Ernst Schröder;
- Abstract algebraic logic, a branch of contemporary mathematical logic.

Perhaps surprisingly, algebraic logic is the oldest approach to formal logic, arguably beginning with a number of memoranda Leibniz wrote in the 1680s, some of which were published in the 19th century and translated into English by Clarence Lewis in 1918. But nearly all of Leibniz's known work on algebraic logic was published only in 1903, after Louis Couturat discovered it in Leibniz's Nachlass. Parkinson (1966) and Loemker (1969) translated selections from Couturat's volume into English.

Brady (2000) discusses the rich historical connections between algebraic logic and model theory. The founders of model theory, Ernst Schröder and Leopold Loewenheim, were logicians in the algebraic tradition. Alfred Tarski, the founder of set theoretic model theory as a major branch of contemporary mathematical logic, also:

- Co-discovered Lindenbaum-Tarski algebra;
- Invented cylindric algebra;
- Wrote the 1941 paper that revived relation algebra, and that can be seen as the starting point of abstract algebraic logic.

Modern mathematical logic began in 1847, with two pamphlets whose respective authors were Augustus DeMorgan and George Boole. They, and later C.S. Peirce, Hugh MacColl, Frege, Peano, Bertrand Russell, and A. N. Whitehead all shared Leibniz's dream of combining symbolic logic, mathematics, and philosophy. Relation algebra is arguably the culmination of Leibniz's approach to logic. With the exception of some writings by Leopold Loewenheim and Thoralf Skolem, algebraic logic went into eclipse soon after the 1910-13 publication of *Principia Mathematica*, not to revive until Tarski's 1940 reexposition of relation algebra.

Leibniz had no influence on the rise of algebraic logic because his logical writings were little studied before the Parkinson and Loemker translations. Our present understanding of Leibniz the logician stems mainly from the work of Wolfgang Lenzen, summarized in Lenzen (2004).^[1] To see how present-day work in logic and metaphysics can draw inspiration from, and shed light on, Leibniz's thought, see Zalta (2000).^[2]

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External links

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Quantum logic

In quantum mechanics, **quantum logic** is a set of rules for reasoning about propositions which takes the principles of quantum theory into account. This research area and its name originated in the 1936 paper by Garrett Birkhoff and John von Neumann, who were attempting to reconcile the apparent inconsistency of classical boolean logic with the facts concerning the measurement of complementary variables in quantum mechanics, such as position and momentum.

Quantum logic can be formulated either as a modified version of propositional logic or as a noncommutative and non-associative many-valued (MV) logic^{[1] [2] [3] [4] [5]}.

Quantum logic has some properties which clearly distinguish it from classical logic, most notably, the failure of the distributive law of propositional logic:

$$p \text{ and } (q \text{ or } r) = (p \text{ and } q) \text{ or } (p \text{ and } r),$$

where the symbols p , q and r are propositional variables. To illustrate why the distributive law fails, consider a particle moving on a line and let

$$p = \text{"the particle is moving to the right"}$$

$$q = \text{"the particle is in the interval } [-1,1]\text{"}$$

$$r = \text{"the particle is not in the interval } [-1,1]\text{"}$$

then the proposition " q or r " is true, so

$$p \text{ and } (q \text{ or } r) = p$$

On the other hand, the propositions " p and q " and " p and r " are both false, since they assert tighter restrictions on simultaneous values of position and momentum than is allowed by the uncertainty principle. So,

$$(p \text{ and } q) \text{ or } (p \text{ and } r) = \text{false}$$

Thus the distributive law fails.

Quantum logic has been proposed as the correct logic for propositional inference generally, most notably by the philosopher Hilary Putnam, at least at one point in his career. This thesis was an important ingredient in Putnam's paper *Is Logic Empirical?* in which he analysed the epistemological status of the rules of propositional logic. Putnam attributes the idea that anomalies associated to quantum measurements originate with anomalies in the logic of physics itself to the physicist David Finkelstein. However, this idea had been around for some time and had been revived several years earlier by George Mackey's work on group representations and symmetry.

The more common view regarding quantum logic, however, is that it provides a formalism for relating observables, system preparation filters and states. In this view, the quantum logic approach resembles more closely the C*-algebraic approach to quantum mechanics; in fact with some minor technical assumptions it can be subsumed by

it. The similarities of the quantum logic formalism to a system of deductive logic may then be regarded more as a curiosity than as a fact of fundamental philosophical importance. A more modern approach to the structure of quantum logic is to assume that it is a diagram – in the sense of category theory – of classical logics (see David Edwards).

Introduction

In his classic treatise *Mathematical Foundations of Quantum Mechanics*, John von Neumann noted that projections on a Hilbert space can be viewed as propositions about physical observables. The set of principles for manipulating these quantum propositions was called *quantum logic* by von Neumann and Birkhoff. In his book (also called *Mathematical Foundations of Quantum Mechanics*) G. Mackey attempted to provide a set of axioms for this propositional system as an orthocomplemented lattice. Mackey viewed elements of this set as potential *yes or no questions* an observer might ask about the state of a physical system, questions that would be settled by some measurement. Moreover Mackey defined a physical observable in terms of these basic questions. Mackey's axiom system is somewhat unsatisfactory though, since it assumes that the partially ordered set is actually given as the orthocomplemented closed subspace lattice of a separable Hilbert space. Piron, Ludwig and others have attempted to give axiomatizations which do not require such explicit relations to the lattice of subspaces.

The remainder of this article assumes the reader is familiar with the spectral theory of self-adjoint operators on a Hilbert space. However, the main ideas can be understood using the finite-dimensional spectral theorem.

Projections as propositions

The so-called *Hamiltonian* formulations of classical mechanics have three ingredients: *states*, *observables* and *dynamics*. In the simplest case of a single particle moving in $\mathbf{R}^3$, the state space is the position-momentum space $\mathbf{R}^6$. We will merely note here that an observable is some real-valued function f on the state space. Examples of observables are position, momentum or energy of a particle. For classical systems, the value $f(x)$, that is the value of f for some particular system state x , is obtained by a process of measurement of f . The propositions concerning a classical system are generated from basic statements of the form

- Measurement of f yields a value in the interval $[a, b]$ for some real numbers a, b .

It follows easily from this characterization of propositions in classical systems that the corresponding logic is identical to that of some Boolean algebra of subsets of the state space. By logic in this context we mean the rules that relate set operations and ordering relations, such as de Morgan's laws. These are analogous to the rules relating boolean conjunctives and material implication in classical propositional logic. For technical reasons, we will also assume that the algebra of subsets of the state space is that of all Borel sets. The set of propositions is ordered by the natural ordering of sets and has a complementation operation. In terms of observables, the complement of the proposition $\{f \geq a\}$ is $\{f < a\}$.

We summarize these remarks as follows:

- The proposition system of a classical system is a lattice with a distinguished *orthocomplementation* operation: The lattice operations of *meet* and *join* are respectively set intersection and set union. The orthocomplementation operation is set complement. Moreover this lattice is *sequentially complete*, in the sense that any sequence $\{E_i\}_i$ of elements of the lattice has a least upper bound, specifically the set-theoretic union:

$$\text{LUB}(\{E_i\}) = \bigcup_{i=1}^{\infty} E_i.$$

In the Hilbert space formulation of quantum mechanics as presented by von Neumann, a physical observable is represented by some (possibly unbounded) densely-defined self-adjoint operator A on a Hilbert space H . A has a spectral decomposition, which is a projection-valued measure E defined on the Borel subsets of $\mathbf{R}$. In particular, for any bounded Borel function f , the following equation holds:

$$f(A) = \int_{\mathbb{R}} f(\lambda) dE(\lambda).$$

In case f is the indicator function of an interval $[a, b]$, the operator $f(A)$ is a self-adjoint projection, and can be interpreted as the quantum analogue of the classical proposition

- Measurement of A yields a value in the interval $[a, b]$.

The propositional lattice of a quantum mechanical system

This suggests the following quantum mechanical replacement for the orthocomplemented lattice of propositions in classical mechanics. This is essentially Mackey's *Axiom VII*:

- The orthocomplemented lattice $\mathcal{Q}$ of propositions of a quantum mechanical system is the lattice of closed subspaces of a complex Hilbert space H where orthocomplementation of V is the orthogonal complement $V^\perp$.

$\mathcal{Q}$ is also sequentially complete: any pairwise disjoint sequence $\{V_i\}_i$ of elements of $\mathcal{Q}$ has a least upper bound. Here disjointness of W_1 and W_2 means W_2 is a subspace of $W_1^\perp$. The least upper bound of $\{V_i\}_i$ is the closed internal direct sum.

Henceforth we identify elements of $\mathcal{Q}$ with self-adjoint projections on the Hilbert space H .

The structure of $\mathcal{Q}$ immediately points to a difference with the partial order structure of a classical proposition system. In the classical case, given a proposition p , the equations

$$I = p \vee q$$

$$0 = p \wedge q$$

have exactly one solution, namely the set-theoretic complement of p . In these equations I refers to the atomic proposition which is identically true and 0 the atomic proposition which is identically false. In the case of the lattice of projections there are infinitely many solutions to the above equations.

Having made these preliminary remarks, we turn everything around and attempt to define observables within the projection lattice framework and using this definition establish the correspondence between self-adjoint operators and observables: A *Mackey observable* is a countably additive homomorphism from the orthocomplemented lattice of the Borel subsets of $\mathbf{R}$ to $\mathcal{Q}$. To say the mapping φ is a countably additive homomorphism means that for any sequence $\{S_i\}_i$ of pairwise disjoint Borel subsets of $\mathbf{R}$, $\{\varphi(S_i)\}_i$ are pairwise orthogonal projections and

$$\varphi\left(\bigcup_{i=1}^{\infty} S_i\right) = \sum_{i=1}^{\infty} \varphi(S_i).$$

Theorem. There is a bijective correspondence between Mackey observables and densely-defined self-adjoint operators on H .

This is the content of the spectral theorem as stated in terms of spectral measures.

Statistical structure

Imagine a forensics lab which has some apparatus to measure the speed of a bullet fired from a gun. Under carefully controlled conditions of temperature, humidity, pressure and so on the same gun is fired repeatedly and speed measurements taken. This produces some distribution of speeds. Though we will not get exactly the same value for each individual measurement, for each cluster of measurements, we would expect the experiment to lead to the same distribution of speeds. In particular, we can expect to assign probability distributions to propositions such as $\{a \leq \text{speed} \leq b\}$. This leads naturally to propose that under controlled conditions of preparation, the measurement of a classical system can be described by a probability measure on the state space. This same statistical structure is also present in quantum mechanics.

A *quantum probability measure* is a function P defined on Q with values in $[0,1]$ such that $P(0)=0$, $P(I)=1$ and if $\{E_i\}_i$ is a sequence of pairwise orthogonal elements of Q then

$$P\left(\sum_{i=1}^{\infty} E_i\right) = \sum_{i=1}^{\infty} P(E_i).$$

The following highly non-trivial theorem is due to Andrew Gleason:

Theorem. Suppose H is a separable Hilbert space of complex dimension at least 3. Then for any quantum probability measure on Q there exists a unique trace class operator S such that

$$P(E) = \text{Tr}(SE)$$

for any self-adjoint projection E .

The operator S is necessarily non-negative (that is all eigenvalues are non-negative) and of trace 1. Such an operator is often called a *density operator*.

Physicists commonly regard a density operator as being represented by a (possibly infinite) density matrix relative to some orthonormal basis.

For more information on statistics of quantum systems, see quantum statistical mechanics.

Automorphisms

An *automorphism* of Q is a bijective mapping $\alpha:Q \rightarrow Q$ which preserves the orthocomplemented structure of Q , that is

$$\alpha\left(\sum_{i=1}^{\infty} E_i\right) = \sum_{i=1}^{\infty} \alpha(E_i)$$

for any sequence $\{E_i\}_i$ of pairwise orthogonal self-adjoint projections. Note that this property implies monotonicity of α . If P is a quantum probability measure on Q , then $E \rightarrow \alpha(E)$ is also a quantum probability measure on Q . By the Gleason theorem characterizing quantum probability measures quoted above, any automorphism α induces a mapping α^* on the density operators by the following formula:

$$\text{Tr}(\alpha^*(S)E) = \text{Tr}(S\alpha(E)).$$

The mapping α^* is bijective and preserves convex combinations of density operators. This means

$$\alpha^*(r_1 S_1 + r_2 S_2) = r_1 \alpha^*(S_1) + r_2 \alpha^*(S_2)$$

whenever $1 = r_1 + r_2$ and r_1, r_2 are non-negative real numbers. Now we use a theorem of Richard V. Kadison:

Theorem. Suppose β is a bijective map from density operators to density operators which is convexity preserving. Then there is an operator U on the Hilbert space which is either linear or conjugate-linear, preserves the inner product and is such that

$$\beta(S) = USU^*$$

for every density operator S . In the first case we say U is unitary, in the second case U is anti-unitary.

Remark. This note is included for technical accuracy only, and should not concern most readers. The result quoted above is not directly stated in Kadison's paper, but can be reduced to it by noting first that β extends to a positive trace preserving map on the trace class operators, then applying duality and finally applying a result of Kadison's paper.

The operator U is not quite unique; if r is a complex scalar of modulus 1, then rU will be unitary or anti-unitary if U is and will implement the same automorphism. In fact, this is the only ambiguity possible.

It follows that automorphisms of Q are in bijective correspondence to unitary or anti-unitary operators modulo multiplication by scalars of modulus 1. Moreover, we can regard automorphisms in two equivalent ways: as operating on states (represented as density operators) or as operating on Q .

Non-relativistic dynamics

In non-relativistic physical systems, there is no ambiguity in referring to time evolution since there is a global time parameter. Moreover an isolated quantum system evolves in a deterministic way: if the system is in a state S at time t then at time $s > t$, the system is in a state $F_{s,t}(S)$. Moreover, we assume

- The dependence is reversible: The operators $F_{s,t}$ are bijective.
- The dependence is homogeneous: $F_{s,t} = F_{s-t,0}$.
- The dependence is convexity preserving: That is, each $F_{s,t}(S)$ is convexity preserving.
- The dependence is weakly continuous: The mapping $\mathbf{R} \rightarrow \mathbf{R}$ given by $t \rightarrow \text{Tr}(F_{s,t}(S) E)$ is continuous for every E in $\mathcal{Q}$.

By Kadison's theorem, there is a 1-parameter family of unitary or anti-unitary operators $\{U_t\}_t$ such that

$$F_{s,t}(S) = U_{s-t} S U_{s-t}^*$$

In fact,

Theorem. Under the above assumptions, there is a strongly continuous 1-parameter group of unitary operators $\{U_t\}_t$ such that the above equation holds.

Note that it easily from uniqueness from Kadison's theorem that

$$U_{t+s} = \sigma(t, s) U_t U_s$$

where $\sigma(t, s)$ has modulus 1. Now the square of an anti-unitary is a unitary, so that all the U_t are unitary. The remainder of the argument shows that $\sigma(t, s)$ can be chosen to be 1 (by modifying each U_t by a scalar of modulus 1.)

Pure states

A convex combination of statistical states S_1 and S_2 is a state of the form $S = p_1 S_1 + p_2 S_2$ where p_1, p_2 are non-negative and $p_1 + p_2 = 1$. Considering the statistical state of system as specified by lab conditions used for its preparation, the convex combination S can be regarded as the state formed in the following way: toss a biased coin with outcome probabilities p_1, p_2 and depending on outcome choose system prepared to S_1 or S_2 .

Density operators form a convex set. The convex set of density operators has extreme points; these are the density operators given by a projection onto a one-dimensional space. To see that any extreme point is such a projection, note that by the spectral theorem S can be represented by a diagonal matrix; since S is non-negative all the entries are non-negative and since S has trace 1, the diagonal entries must add up to 1. Now if it happens that the diagonal matrix has more than one non-zero entry it is clear that we can express it as a convex combination of other density operators.

The extreme points of the set of density operators are called pure states. If S is the projection on the 1-dimensional space generated by a vector ψ of norm 1 then

$$\text{Tr}(SE) = \langle E\psi | \psi \rangle$$

for any E in $\mathcal{Q}$. In physics jargon, if

$$S = |\psi\rangle\langle\psi|,$$

where ψ has norm 1, then

$$\text{Tr}(SE) = \langle \psi | E | \psi \rangle.$$

Thus pure states can be identified with *rays* in the Hilbert space H .

The measurement process

Consider a quantum mechanical system with lattice Q which is in some statistical state given by a density operator S . This essentially means an ensemble of systems specified by a repeatable lab preparation process. The result of a cluster of measurements intended to determine the truth value of proposition E , is just as in the classical case, a probability distribution of truth values **T** and **F**. Say the probabilities are p for **T** and $q = 1 - p$ for **F**. By the previous section $p = \text{Tr}(SE)$ and $q = \text{Tr}(S(I - E))$.

Perhaps the most fundamental difference between classical and quantum systems is the following: regardless of what process is used to determine E immediately after the measurement the system will be in one of two statistical states:

- If the result of the measurement is **T**

$$\frac{1}{\text{Tr}(ES)}ESE.$$

- If the result of the measurement is **F**

$$\frac{1}{\text{Tr}((I - E)S)}(I - E)S(I - E).$$

(We leave to the reader the handling of the degenerate cases in which the denominators may be 0.) We now form the convex combination of these two ensembles using the relative frequencies p and q . We thus obtain the result that the measurement process applied to a statistical ensemble in state S yields another ensemble in statistical state:

$$M_E(S) = ESE + (I - E)S(I - E).$$

We see that a pure ensemble becomes a mixed ensemble after measurement. Measurement, as described above, is a special case of quantum operations.

Limitations

Quantum logic derived from propositional logic provides a satisfactory foundation for a theory of reversible quantum processes. Examples of such processes are the covariance transformations relating two frames of reference, such as change of time parameter or the transformations of special relativity. Quantum logic also provides a satisfactory understanding of density matrices. Quantum logic can be stretched to account for some kinds of measurement processes corresponding to answering yes-no questions about the state of a quantum system. However, for more general kinds of measurement operations (that is quantum operations), a more complete theory of filtering processes is necessary. Such an approach is provided by the consistent histories formalism. On the other hand, quantum logics derived from MV-logic extend its range of applicability to irreversible quantum processes and/or 'open' quantum systems.

In any case, these quantum logic formalisms must be generalized in order to deal with super-geometry (which is needed to handle Fermi-fields) and non-commutative geometry (which is needed in string theory and quantum gravity theory). Both of these theories use a partial algebra with an "integral" or "trace". The elements of the partial algebra are not observables; instead the "trace" yields "greens functions" which generate scattering amplitudes. One thus obtains a local S-matrix theory (see D. Edwards).

Since around 1978 the Flato school (see F. Bayen) has been developing an alternative to the quantum logics approach called deformation quantization (see Weyl quantization).

In 2004, Prakash Panangaden described how to capture the kinematics of quantum causal evolution using System BV, a deep inference logic originally developed for use in structural proof theory.^[6] Alessio Guglielmi, Lutz Straßburger, and Richard Blute have also done work in this area.^[7]

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See also

- Mathematical formulation of quantum mechanics
- Multi-valued logic
- Quasi-set theory
- HPO formalism (An approach to temporal quantum logic)
- Quantum field theory

Further reading

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External links

- Stanford Encyclopedia of Philosophy entry on Quantum Logic and Probability Theory (<http://plato.stanford.edu/entries/qt-quantlog/>)

Quantum computer

A **quantum computer** is a device for computation that makes direct use of quantum mechanical phenomena, such as superposition and entanglement, to perform operations on data. Quantum computers are different from traditional computers based on transistors. The basic principle behind quantum computation is that quantum properties can be used to represent data and perform operations on these data.^[1] A theoretical model is the quantum Turing machine, also known as the universal quantum computer.

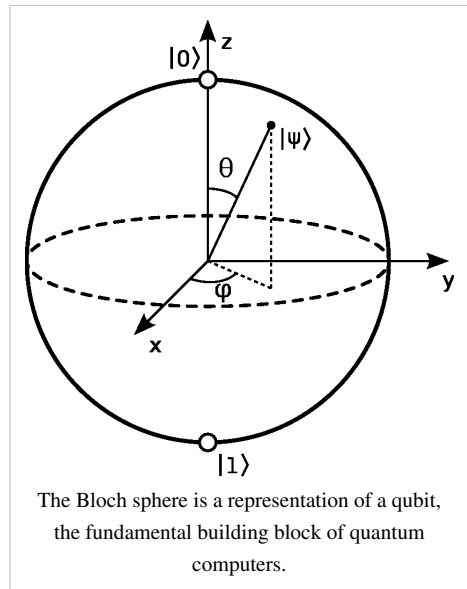
Although quantum computing is still in its infancy, experiments have been carried out in which quantum computational operations were executed on a very small number of qubits (quantum bit). Both practical and theoretical research continues, and many national government and military funding agencies support quantum computing research to develop quantum computers for both civilian and national security purposes, such as cryptanalysis.^[2]

If large-scale quantum computers can be built, they will be able to solve certain problems much faster than any current classical computers (for example Shor's algorithm). Quantum computers do not allow the computation of functions that are not theoretically computable by classical computers, i.e. they do not alter the Church–Turing thesis. The gain is only in efficiency.

Basis

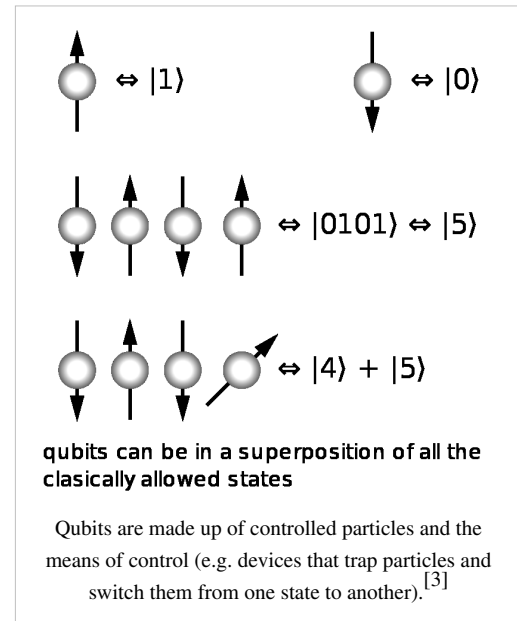
A classical computer has a memory made up of bits, where each bit represents either a one or a zero. A quantum computer maintains a sequence of qubits. A single qubit can represent a one, a zero, or, crucially, any quantum superposition of these; moreover, a pair of qubits can be in any quantum superposition of 4 states, and three qubits in any superposition of 8. In general a quantum computer with n qubits can be in an arbitrary superposition of up to 2^n different states simultaneously (this compares to a normal computer that can only be in *one* of these 2^n states at any one time). A quantum computer operates by manipulating those qubits with a fixed sequence of quantum logic gates. The sequence of gates to be applied is called a quantum algorithm.

An example of an implementation of qubits for a quantum computer could start with the use of particles with two spin states: "down" and "up" (typically written $|\downarrow\rangle$ and $|\uparrow\rangle$, or $|0\rangle$ and $|1\rangle$). But in fact any system possessing an observable quantity A which is *conserved* under time evolution and such that A has at least two discrete and sufficiently spaced consecutive eigenvalues, is a suitable candidate for implementing a qubit. This is true because any such system can be mapped onto an effective spin-1/2 system.



Bits vs. qubits

Consider first a classical computer that operates on a three-bit register. The state of the computer at any time is a probability distribution over the $2^3 = 8$ different three-bit strings 000, 001, 010, 011, 100, 101, 110, 111. If it is a deterministic computer, then it is in exactly one of these states with probability 1. However, if it is a probabilistic computer, then there is a possibility of it being in any *one* of a number of different states. We can describe this probabilistic state by eight nonnegative numbers a, b, c, d, e, f, g, h (where a = probability computer is in state 000, b = probability computer is in state 001, etc.). There is a restriction that these probabilities sum to 1.



The state of a three-qubit quantum computer is similarly described by an eight-dimensional vector (a, b, c, d, e, f, g, h) , called a ket. However, instead of adding to one, the sum of the *squares* of the coefficient magnitudes, $|a|^2 + |b|^2 + \dots + |h|^2$, must equal one. Moreover, the coefficients are complex numbers. Since states are represented by complex wavefunctions, two states being added together will undergo interference. This is a key difference between quantum computing and probabilistic classical computing.^[4]

If you measure the three qubits, then you will observe a three-bit string. The probability of measuring a string will equal the squared magnitude of that string's coefficients (using our example, probability that we read state as 000 = $|a|^2$, probability that we read state as 001 = $|b|^2$, etc.). Thus a measurement of the quantum state with coefficients $(a, b, \dots, h)$ gives the classical probability distribution $(|a|^2, |b|^2, \dots, |h|^2)$. We say that the quantum state "collapses" to a classical state.

Note that an eight-dimensional vector can be specified in many different ways, depending on what basis you choose for the space. The basis of three-bit strings 000, 001, ..., 111 is known as the computational basis, and is often convenient, but other bases of unit-length, orthogonal vectors can also be used. Ket notation is often used to make explicit the choice of basis. For example, the state (a, b, c, d, e, f, g, h) in the computational basis can be written as

$$a|000\rangle + b|001\rangle + c|010\rangle + d|011\rangle + e|100\rangle + f|101\rangle + g|110\rangle + h|111\rangle, \text{ where, e.g., } |010\rangle = (0, 0, 1, 0, 0, 0, 0, 0).$$

The computational basis for a single qubit (two dimensions) is $|0\rangle = (1, 0)$, $|1\rangle = (0, 1)$, but another common basis are the eigenvectors of the Pauli-x operator: $|+\rangle = \frac{1}{\sqrt{2}}(1, 1)$ and $|-\rangle = \frac{1}{\sqrt{2}}(1, -1)$.

Note that although recording a classical state of n bits, a 2^n -dimensional probability distribution, requires an exponential number of real numbers, practically we can always think of the system as being exactly one of the n -bit strings—we just don't know which one. Quantum mechanically, this is not the case, and all 2^n complex coefficients need to be kept track of to see how the quantum system evolves. For example, a 300-qubit quantum computer has a state described by 2^{300} (approximately 10^{90}) complex numbers, more than the number of atoms in the observable universe.

Operation

While a classical three-bit state and a quantum three-qubit state are both eight-dimensional vectors, they are manipulated quite differently for classical or quantum computation. For computing in either case, the system must be initialized, for example into the all-zeros string, $|000\rangle$, corresponding to the vector $(1,0,0,0,0,0,0,0)$. In classical randomized computation, the system evolves according to the application of stochastic matrices, which preserve that the probabilities add up to one (i.e., preserve the L1 norm). In quantum computation, on the other hand, allowed operations are unitary matrices, which are effectively rotations (they preserve that the sum of the squares add up to one, the Euclidean or L2 norm). (Exactly what unitaries can be applied depend on the physics of the quantum device.) Consequently, since rotations can be undone by rotating backward, quantum computations are reversible. (Technically, quantum operations can be probabilistic combinations of unitaries, so quantum computation really does generalize classical computation. See quantum circuit for a more precise formulation.)

Finally, upon termination of the algorithm, the result needs to be read off. In the case of a classical computer, we *sample* from the probability distribution on the three-bit register to obtain one definite three-bit string, say 000. Quantum mechanically, we *measure* the three-qubit state, which is equivalent to collapsing the quantum state down to a classical distribution (with the coefficients in the classical state being the squared magnitudes of the coefficients for the quantum state, as described above) followed by sampling from that distribution. Note that this destroys the original quantum state. Many algorithms will only give the correct answer with a certain probability, however by repeatedly initializing, running and measuring the quantum computer, the probability of getting the correct answer can be increased.

For more details on the sequences of operations used for various quantum algorithms, see universal quantum computer, Shor's algorithm, Grover's algorithm, Deutsch-Jozsa algorithm, amplitude amplification, quantum Fourier transform, quantum gate, quantum adiabatic algorithm and quantum error correction.

Potential

Integer factorization is believed to be computationally infeasible with an ordinary computer for large integers if they are the product of few prime numbers (e.g., products of two 300-digit primes).^[5] By comparison, a quantum computer could efficiently solve this problem using Shor's algorithm to find its factors. This ability would allow a quantum computer to decrypt many of the cryptographic systems in use today, in the sense that there would be a polynomial time (in the number of digits of the integer) algorithm for solving the problem. In particular, most of the popular public key ciphers are based on the difficulty of factoring integers (or the related discrete logarithm problem which can also be solved by Shor's algorithm), including forms of RSA. These are used to protect secure Web pages, encrypted email, and many other types of data. Breaking these would have significant ramifications for electronic privacy and security.

However, other existing cryptographic algorithms don't appear to be broken by these algorithms.^[6] ^[7] Some public-key algorithms are based on problems other than the integer factorization and discrete logarithm problems to which Shor's algorithm applies, like the McEliece cryptosystem based on a problem in coding theory.^[6] ^[8] Lattice based cryptosystems are also not known to be broken by quantum computers, and finding a polynomial time algorithm for solving the dihedral hidden subgroup problem, which would break many lattice based cryptosystems, is a well-studied open problem.^[9] It has been proven that applying Grover's algorithm to break a symmetric (secret key) algorithm by brute force requires roughly $2^{n/2}$ invocations of the underlying cryptographic algorithm, compared with roughly 2^n in the classical case,^[10] meaning that symmetric key lengths are effectively halved: AES-256 would have the same security against an attack using Grover's algorithm that AES-128 has against classical brute-force search (see Key size). Quantum cryptography could potentially fulfill some of the functions of public key cryptography.

Besides factorization and discrete logarithms, quantum algorithms offering a more than polynomial speedup over the best known classical algorithm have been found for several problems,^[11] including the simulation of quantum physical processes from chemistry and solid state physics, the approximation of Jones polynomials, and solving Pell's equation. No mathematical proof has been found that shows that an equally fast classical algorithm cannot be discovered, although this is considered unlikely. For some problems, quantum computers offer a polynomial speedup. The most well-known example of this is *quantum database search*, which can be solved by Grover's algorithm using quadratically fewer queries to the database than are required by classical algorithms. In this case the advantage is provable. Several other examples of provable quantum speedups for query problems have subsequently been discovered, such as for finding collisions in two-to-one functions and evaluating NAND trees.

Consider a problem that has these four properties:

1. The only way to solve it is to guess answers repeatedly and check them,
2. There are n possible answers to check,
3. Every possible answer takes the same amount of time to check, and
4. There are no clues about which answers might be better: generating possibilities randomly is just as good as checking them in some special order.

An example of this is a password cracker that attempts to guess the password for an encrypted file (assuming that the password has a maximum possible length).

For problems with all four properties, the time for a quantum computer to solve this will be proportional to the square root of n . That can be a very large speedup, reducing some problems from years to seconds. It can be used to attack symmetric ciphers such as Triple DES and AES by attempting to guess the secret key.

Grover's algorithm can also be used to obtain a quadratic speed-up [over a brute-force search] for a class of problems known as NP-complete.

Since chemistry and nanotechnology rely on understanding quantum systems, and such systems are impossible to simulate in an efficient manner classically, many believe quantum simulation will be one of the most important applications of quantum computing.^[12]

There are a number of practical difficulties in building a quantum computer, and thus far quantum computers have only solved trivial problems. David DiVincenzo, of IBM, listed the following requirements for a practical quantum computer:^[13]

- scalable physically to increase the number of qubits;
- qubits can be initialized to arbitrary values;
- quantum gates faster than decoherence time;
- universal gate set;
- qubits can be read easily.

Quantum decoherence

One of the greatest challenges is controlling or removing quantum decoherence. This usually means isolating the system from its environment as the slightest interaction with the external world would cause the system to decohere. This effect is irreversible, as it is non-unitary, and is usually something that should be highly controlled, if not avoided. Decoherence times for candidate systems, in particular the transverse relaxation time T_2 (for NMR and MRI technology, also called the *dephasing time*), typically range between nanoseconds and seconds at low temperature.^[4]

These issues are more difficult for optical approaches as the timescales are orders of magnitude shorter and an often-cited approach to overcoming them is optical pulse shaping. Error rates are typically proportional to the ratio of operating time to decoherence time, hence any operation must be completed much more quickly than the decoherence time.

If the error rate is small enough, it is thought to be possible to use quantum error correction, which corrects errors due to decoherence, thereby allowing the total calculation time to be longer than the decoherence time. An often cited figure for required error rate in each gate is 10^{-4} . This implies that each gate must be able to perform its task in one 10,000th of the decoherence time of the system.

Meeting this scalability condition is possible for a wide range of systems. However, the use of error correction brings with it the cost of a greatly increased number of required qubits. The number required to factor integers using Shor's algorithm is still polynomial, and thought to be between L and L^2 , where L is the number of bits in the number to be factored; error correction algorithms would inflate this figure by an additional factor of L . For a 1000-bit number, this implies a need for about 10^4 qubits without error correction.^[14] With error correction, the figure would rise to about 10^7 qubits. Note that computation time is about L^2 or about 10^7 steps and on 1 MHz, about 10 seconds.

A very different approach to the stability-decoherence problem is to create a topological quantum computer with anyons, quasi-particles used as threads and relying on braid theory to form stable logic gates.^{[15] [16]}

Developments

There are a number of quantum computing candidates, among those:

- Superconductor-based quantum computers (including SQUID-based quantum computers)^[17]
- Trapped ion quantum computer
- Optical lattices
- Topological quantum computer^[18]
- Quantum dot on surface (e.g. the Loss-DiVincenzo quantum computer)
- Nuclear magnetic resonance on molecules in solution (liquid NMR)
- Solid state NMR Kane quantum computers
- Electrons on helium quantum computers
- Cavity quantum electrodynamics (CQED)
- Molecular magnet
- Fullerene-based ESR quantum computer
- Optic-based quantum computers (Quantum optics)
- Diamond-based quantum computer^{[19] [20] [21]}
- Bose–Einstein condensate-based quantum computer^[22]
- Transistor-based quantum computer - string quantum computers with entrainment of positive holes using an electrostatic trap
- Spin-based quantum computer
- Adiabatic quantum computation^[23]
- Rare-earth-metal-ion-doped inorganic crystal based quantum computers^{[24] [25]}

The large number of candidates demonstrates that the topic, in spite of rapid progress, is still in its infancy. But at the same time there is also a vast amount of flexibility.

In 2005, researchers at the University of Michigan built a semiconductor chip which functioned as an ion trap. Such devices, produced by standard lithography techniques, may point the way to scalable quantum computing tools.^[26] An improved version was made in 2006.

In 2009, researchers at Yale University created the first rudimentary solid-state quantum processor. The two-qubit superconducting chip was able to run elementary algorithms. Each of the two artificial atoms (or qubits) were made up of a billion aluminum atoms but they acted like a single one that could occupy two different energy states.^{[27] [28]}

Another team, working at the University of Bristol, also created a silicon-based quantum computing chip, based on quantum optics. The team was able to run Shor's algorithm on the chip.^[29] The latest developments [for 2010] can be found in ^[30].

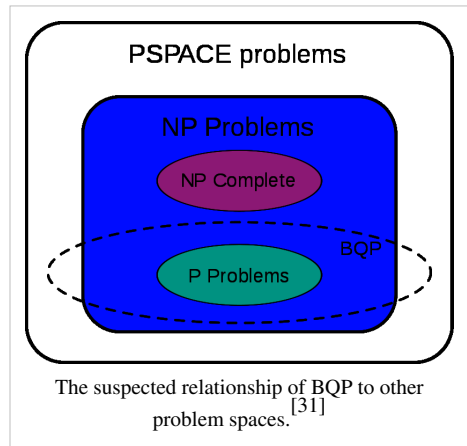
Relation to computational complexity theory

The class of problems that can be efficiently solved by quantum computers is called BQP, for "bounded error, quantum, polynomial time". Quantum computers only run probabilistic algorithms, so BQP on quantum computers is the counterpart of BPP ("bounded error, probabilistic, polynomial time") on classical computers. It is defined as the set of problems solvable with a polynomial-time algorithm, whose probability of error is bounded away from one half.^[32] A quantum computer is said to "solve" a problem if, for every instance, its answer will be right with high probability. If that solution runs in polynomial time, then that problem is in BQP.

BQP is contained in the complexity class $\#P$ (or more precisely in the associated class of decision problems $P^{\#P}$),^[33] which is a subclass of PSPACE.

BQP is suspected to be disjoint from NP-complete and a strict superset of P, but that is not known. Both integer factorization and discrete log are in BQP. Both of these problems are NP problems suspected to be outside BPP, and hence outside P. Both are suspected to not be NP-complete. There is a common misconception that quantum computers can solve NP-complete problems in polynomial time. That is not known to be true, and is generally suspected to be false.^[33]

Although quantum computers may be faster than classical computers, those described above can't solve any problems that classical computers can't solve, given enough time and memory (however, those amounts might be practically infeasible). A Turing machine can simulate these quantum computers, so such a quantum computer could never solve an undecidable problem like the halting problem. The existence of "standard" quantum computers does not disprove the Church–Turing thesis.^[34] It has been speculated that theories of quantum gravity, such as M-theory or loop quantum gravity, may allow even faster computers to be built. Currently, it's an open problem to even *define* computation in such theories due to the problem of time, i.e. there's no obvious way to describe what it means for an observer to submit input to a computer and later receive output.^[35]



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 - jQuantum: Java quantum circuit simulator (<http://jquantum.sourceforge.net/jQuantumApplet.html>)
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 - Online lecture on An Introduction to Quantum Computing, Edward Gerjuoy (2008) (<http://nanohub.org/resources/4778>)
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Quantum chemistry

Quantum chemistry is a branch of theoretical chemistry which applies quantum mechanics and quantum field theory to address problems in chemistry. One application of quantum chemistry is the electronic behavior of atoms and molecules relative to their chemical reactivity. Quantum chemistry lies on the border between chemistry and physics. Thus, significant contributions have been made by scientists from both fields. It has a strong and active overlap with the field of atomic physics and molecular physics, as well as physical chemistry.

Quantum chemistry mathematically describes the fundamental behavior of matter at the molecular scale^[1], but can span from elementary particles such as electrons (fermions) and photons (bosons) to the cosmos such as star-formation^[2]. It is, in principle, possible to describe all chemical systems using this theory. In practice, only the simplest chemical systems may realistically be investigated in purely quantum mechanical terms, and approximations must be made for most practical purposes (e.g., Hartree-Fock, post Hartree-Fock or Density functional theory, see computational chemistry for more details). Hence a detailed understanding of quantum mechanics is not necessary for most chemistry, as the important implications of the theory (principally the orbital approximation) can be understood and applied in simpler terms.

In quantum mechanics the Hamiltonian, or the physical state, of a particle can be expressed as the sum of two operators, one corresponding to kinetic energy and the other to potential energy. The Hamiltonian in the Schrödinger wave equation used in quantum chemistry does not contain terms for the spin of the electron.

Solutions of the Schrödinger equation for the hydrogen atom gives the form of the wave function for atomic orbitals, and the relative energy of the various orbitals. The orbital approximation can be used to understand the other atoms e.g. helium, lithium and carbon.

History

The history of quantum chemistry essentially began with the 1838 discovery of cathode rays by Michael Faraday, the 1859 statement of the black body radiation problem by Gustav Kirchhoff, the 1877 suggestion by Ludwig Boltzmann that the energy states of a physical system could be discrete, and the 1900 quantum hypothesis by Max Planck that any energy radiating atomic system can theoretically be divided into a number of discrete energy elements ϵ such that each of these energy elements is proportional to the frequency ν with which they each individually radiate energy, as defined by the following formula:

$$\epsilon = h\nu$$

where h is a numerical value called Planck's Constant. Then, in 1905, to explain the photoelectric effect (1839), i.e., that shining light on certain materials can function to eject electrons from the material, Albert Einstein postulated, based on Planck's quantum hypothesis, that light itself consists of individual quantum particles, which later came to be called photons (1926). In the years to follow, this theoretical basis slowly began to be applied to chemical structure, reactivity, and bonding.

Electronic structure

The first step in solving a quantum chemical problem is usually solving the Schrödinger equation (or Dirac equation in relativistic quantum chemistry) with the electronic molecular Hamiltonian. This is called determining the **electronic structure** of the molecule. It can be said that the electronic structure of a molecule or crystal implies essentially its chemical properties. An exact solution for the Schrödinger equation can only be obtained for the hydrogen atom. Since all other atomic, or molecular systems, involve the motions of three or more "particles", their Schrödinger equations cannot be solved exactly and so approximate solutions must be sought.

Wave model

The foundation of quantum mechanics and quantum chemistry is the **wave model**, in which the atom is a small, dense, positively charged nucleus surrounded by electrons. Unlike the earlier Bohr model of the atom, however, the wave model describes electrons as "clouds" moving in orbitals, and their positions are represented by probability distributions rather than discrete points. The strength of this model lies in its predictive power. Specifically, it predicts the pattern of chemically similar elements found in the periodic table. The wave model is so named because electrons exhibit properties (such as interference) traditionally associated with waves. See wave-particle duality.

Valence bond

Although the mathematical basis of quantum chemistry had been laid by Schrödinger in 1926, it is generally accepted that the first true calculation in quantum chemistry was that of the German physicists Walter Heitler and Fritz London on the hydrogen (H_2) molecule in 1927. Heitler and London's method was extended by the American theoretical physicist John C. Slater and the American theoretical chemist Linus Pauling to become the **Valence-Bond (VB)** [or **Heitler-London-Slater-Pauling (HLSP)**] method. In this method, attention is primarily devoted to the pairwise interactions between atoms, and this method therefore correlates closely with classical chemists' drawings of bonds.

Molecular orbital

An alternative approach was developed in 1929 by Friedrich Hund and Robert S. Mulliken, in which electrons are described by mathematical functions delocalized over an entire molecule. The **Hund-Mulliken** approach or **molecular orbital (MO) method** is less intuitive to chemists, but has turned out capable of predicting spectroscopic properties better than the VB method. This approach is the conceptional basis of the **Hartree-Fock method** and further post Hartree-Fock methods.

Density functional theory

The **Thomas-Fermi model** was developed independently by Thomas and Fermi in 1927. This was the first attempt to describe many-electron systems on the basis of electronic density instead of wave functions, although it was not very successful in the treatment of entire molecules. The method did provide the basis for what is now known as **density functional theory**. Though this method is less developed than post Hartree-Fock methods, its significantly lower computational requirements (scaling typically no worse than n^3 with respect to n basis functions) allow it to tackle larger polyatomic molecules and even macromolecules. This computational affordability and often comparable accuracy to MP2 and CCSD (post-Hartree-Fock methods) has made it one of the most popular methods in computational chemistry at present.

Chemical dynamics

A further step can consist of solving the Schrödinger equation with the total molecular Hamiltonian in order to study the motion of molecules. Direct solution of the Schrödinger equation is called *quantum molecular dynamics*, within the semiclassical approximation *semiclassical molecular dynamics*, and within the classical mechanics framework *molecular dynamics (MD)*. Statistical approaches, using for example Monte Carlo methods, are also possible.

Adiabatic chemical dynamics

In **adiabatic dynamics**, interatomic interactions are represented by single scalar potentials called potential energy surfaces. This is the Born-Oppenheimer approximation introduced by Born and Oppenheimer in 1927. Pioneering applications of this in chemistry were performed by Rice and Ramsperger in 1927 and Kassel in 1928, and generalized into the RRKM theory in 1952 by Marcus who took the transition state theory developed by Eyring in

1935 into account. These methods enable simple estimates of unimolecular reaction rates from a few characteristics of the potential surface.

Non-adiabatic chemical dynamics

Non-adiabatic dynamics consists of taking the interaction between several coupled potential energy surface (corresponding to different electronic quantum states of the molecule). The coupling terms are called **vibronic couplings**. The pioneering work in this field was done by Stueckelberg, Landau, and Zener in the 1930s, in their work on what is now known as the Landau-Zener transition. Their formula allows the transition probability between two diabatic potential curves in the neighborhood of an avoided crossing to be calculated.

Quantum chemistry and quantum field theory

The application of quantum field theory (QFT) to chemical systems and theories has become increasingly common in the modern physical sciences. One of the first and most fundamentally explicit appearances of this is seen in the theory of the photomagnetron. In this system, plasmas, which are ubiquitous in both physics and chemistry, are studied in order to determine the basic quantization of the underlying bosonic field. However, quantum field theory is of interest in many fields of chemistry, including: nuclear chemistry, astrochemistry, sonochemistry, and quantum hydrodynamics. Field theoretic methods have also been critical in developing the ab initio Effective Hamiltonian theory of semi-empirical pi-electron methods.

See also

- Atomic physics
- Computational chemistry
- Condensed matter physics
- International Academy of Quantum Molecular Science
- Molecular modelling
- Physical chemistry
- Quantum chemistry computer programs
- Quantum electrochemistry
- QMC@Home
- Theoretical physics

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External links

- The Sherrill Group - Notes (<http://vergil.chemistry.gatech.edu/notes/index.html>)
- ChemViz Curriculum Support Resources (<http://www.shodor.org/chemviz/>)
- Early ideas in the history of quantum chemistry (<http://www.quantum-chemistry-history.com/>)
- The Particle Adventure (<http://particleadventure.org/>)

Nobel lectures by quantum chemists

- Walter Kohn's Nobel lecture (<http://nobelprize.org/chemistry/laureates/1998/kohn-lecture.html>)
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Density functional theory

Density functional theory (DFT) is a quantum mechanical theory used in physics and chemistry to investigate the electronic structure (principally the ground state) of many-body systems, in particular atoms, molecules, and the condensed phases. With this theory, the properties of a many-electron system can be determined by using functionals, i.e. functions of another function, which in this case is the spatially dependent electron density. Hence the name density functional theory comes from the use of functionals of the electron density. DFT is among the most popular and versatile methods available in condensed-matter physics, computational physics, and computational chemistry.

DFT has been very popular for calculations in solid state physics since the 1970s. However, DFT was not considered accurate enough for calculations in quantum chemistry until the 1990s, when the approximations used in the theory were greatly refined to better model the exchange and correlation interactions. In many cases the results of DFT calculations for solid-state systems agree quite satisfactorily with experimental data. Computational costs are relatively low when compared to traditional ways based on the complicated many-electron wavefunction, such as Hartree-Fock theory and its descendants. DFT is now a leading method for electronic structure calculations in chemistry and solid-state physics.

Despite recent improvements, there are still difficulties in using density functional theory to properly describe intermolecular interactions, especially van der Waals forces (dispersion); charge transfer excitations; transition states, global potential energy surfaces and some other strongly correlated systems; and in calculations of the band gap in semiconductors. Its incomplete treatment of dispersion can adversely affect the accuracy of DFT (at least when used alone and uncorrected) in the treatment of systems which are dominated by dispersion (e.g. interacting noble gas atoms)^[1] or where dispersion competes significantly with other effects (e.g. in biomolecules).^[2] The development of new DFT methods designed to overcome this problem, by alterations to the functional^[3] or by the inclusion of additive terms,^{[4] [5] [6]} is a current research topic.

Overview of method

Although density functional theory has its conceptual roots in the Thomas-Fermi model, DFT was put on a firm theoretical footing by the two **Hohenberg-Kohn theorems** (H-K).^[7] The original H-K theorems held only for non-degenerate ground states in the absence of a magnetic field, although they have since been generalized to encompass these.^{[8] [9]}

The first H-K theorem demonstrates that the ground state properties of a many-electron system are uniquely determined by an electron density that depends on only 3 spatial coordinates. It lays the groundwork for reducing the many-body problem of N electrons with $3N$ spatial coordinates to 3 spatial coordinates, through the use of functionals of the electron density. This theorem can be extended to the time-dependent domain to develop time-dependent density functional theory (TDDFT), which can be used to describe excited states.

The second H-K theorem defines an energy functional for the system and proves that the correct ground state electron density minimizes this energy functional.

Within the framework of Kohn-Sham DFT (KS DFT), the intractable many-body problem of interacting electrons in a static external potential is reduced to a tractable problem of non-interacting electrons moving in an effective potential. The effective potential includes the external potential and the effects of the Coulomb interactions between the electrons, e.g., the exchange and correlation interactions. Modeling the latter two interactions becomes the difficulty within KS DFT. The simplest approximation is the local-density approximation (LDA), which is based upon exact exchange energy for a uniform electron gas, which can be obtained from the Thomas-Fermi model, and from fits to the correlation energy for a uniform electron gas. Non-interacting systems are relatively easy to solve as the wavefunction can be represented as a Slater determinant of orbitals. Further, the kinetic energy functional of such

a system is known exactly. The exchange-correlation part of the total-energy functional remains unknown and must be approximated.

Another approach, less popular than KS DFT but arguably more closely related to the spirit of the original H-K theorems, is orbital-free density functional theory (OFDFT), in which approximate functionals are also used for the kinetic energy of the non-interacting system.

Note: Recently, another foundation to construct the DFT without the Hohenberg-Kohn theorems is getting popular, that is, as a Legendre transformation from external potential to electron density. See, e.g., Density Functional Theory -- an introduction^[10], Rev. Mod. Phys. 78, 865–951 (2006)^[11], and references there in. A book, 'The Fundamentals of Density Functional Theory'^[12] written by H.Eschrig, contains detailed mathematical discussions on the DFT; there is a difficulty for N-particle system with infinite volume; however, we have no mathematical problems in finite periodic system (torus).

Derivation and formalism

As usual in many-body electronic structure calculations, the nuclei of the treated molecules or clusters are seen as fixed (the Born-Oppenheimer approximation), generating a static external potential V in which the electrons are moving. A stationary electronic state is then described by a wavefunction $\Psi(\vec{r}_1, \dots, \vec{r}_N)$ satisfying the many-electron time-independent Schrödinger equation

$$\hat{H}\Psi = [\hat{T} + \hat{V} + \hat{U}] \Psi = \left[\sum_i^N -\frac{\hbar^2}{2m} \nabla_i^2 + \sum_i^N V(\vec{r}_i) + \sum_{i<j}^N U(\vec{r}_i, \vec{r}_j) \right] \Psi = E\Psi$$

where, for the N -electron system, $\hat{H}$ is the Hamiltonian, E is the total energy, $\hat{T}$ is the kinetic energy, $\hat{V}$ is the potential energy from the external field due to positively charged nuclei, and $\hat{U}$ is the electron-electron interaction energy. The operators $\hat{T}$ and $\hat{U}$ are called universal operators as they are the same for any N -electron system, while $\hat{V}$ is system dependent. This complicated many-particle equation is not separable into simpler single-particle equations because of the interaction term $\hat{U}$.

There are many sophisticated methods for solving the many-body Schrödinger equation based on the expansion of the wavefunction in Slater determinants. While the simplest one is the Hartree-Fock method, more sophisticated approaches are usually categorized as post-Hartree-Fock methods. However, the problem with these methods is the huge computational effort, which makes it virtually impossible to apply them efficiently to larger, more complex systems.

Here DFT provides an appealing alternative, being much more versatile as it provides a way to systematically map the many-body problem, with $\hat{U}$, onto a single-body problem without $\hat{U}$. In DFT the key variable is the particle density $n(\vec{r})$, which for a normalized Ψ is given by

$$n(\vec{r}) = N \int d^3r_2 \int d^3r_3 \cdots \int d^3r_N \Psi^*(\vec{r}, \vec{r}_2, \dots, \vec{r}_N) \Psi(\vec{r}, \vec{r}_2, \dots, \vec{r}_N).$$

This relation can be reversed, i.e. for a given ground-state density $n_0(\vec{r})$ it is possible, in principle, to calculate the corresponding ground-state wavefunction $\Psi_0(\vec{r}_1, \dots, \vec{r}_N)$. In other words, Ψ_0 is a unique functional of n_0 ,^[7]

$$\Psi_0 = \Psi[n_0]$$

and consequently the ground-state expectation value of an observable $\hat{O}$ is also a functional of n_0

$$O[n_0] = \langle \Psi[n_0] | \hat{O} | \Psi[n_0] \rangle.$$

In particular, the ground-state energy is a functional of n_0

$$E_0 = E[n_0] = \langle \Psi[n_0] | \hat{T} + \hat{V} + \hat{U} | \Psi[n_0] \rangle$$

where the contribution of the external potential $\langle \Psi[n_0] | \hat{V} | \Psi[n_0] \rangle$ can be written explicitly in terms of the ground-state density n_0

$$V[n_0] = \int V(\vec{r}) n_0(\vec{r}) d^3r.$$

More generally, the contribution of the external potential $\langle \Psi | \hat{V} | \Psi \rangle$ can be written explicitly in terms of the density n ,

$$V[n] = \int V(\vec{r}) n(\vec{r}) d^3r.$$

The functionals $T[n]$ and $U[n]$ are called universal functionals, while $V[n]$ is called a non-universal functional, as it depends on the system under study. Having specified a system, i.e., having specified $\hat{V}$, one then has to minimize the functional

$$E[n] = T[n] + U[n] + \int V(\vec{r}) n(\vec{r}) d^3r$$

with respect to $n(\vec{r})$, assuming one has got reliable expressions for $T[n]$ and $U[n]$. A successful minimization of the energy functional will yield the ground-state density n_0 and thus all other ground-state observables.

The variational problems of minimizing the energy functional $E[n]$ can be solved by applying the Lagrangian method of undetermined multipliers.^[13] First, one considers an energy functional that doesn't explicitly have an electron-electron interaction energy term,

$$E_s[n] = \langle \Psi_s[n] | \hat{T}_s + \hat{V}_s | \Psi_s[n] \rangle$$

where $\hat{T}_s$ denotes the non-interacting kinetic energy and $\hat{V}_s$ is an external effective potential in which the particles are moving. Obviously, $n_s(\vec{r}) \stackrel{\text{def}}{=} n(\vec{r})$ if $\hat{V}_s$ is chosen to be

$$\hat{V}_s = \hat{V} + \hat{U} + (\hat{T} - \hat{T}_s).$$

Thus, one can solve the so-called Kohn-Sham equations of this auxiliary non-interacting system,

$$\left[-\frac{\hbar^2}{2m} \nabla^2 + V_s(\vec{r}) \right] \phi_i(\vec{r}) = \epsilon_i \phi_i(\vec{r})$$

which yields the orbitals ϕ_i that reproduce the density $n(\vec{r})$ of the original many-body system

$$n(\vec{r}) \stackrel{\text{def}}{=} n_s(\vec{r}) = \sum_i^N |\phi_i(\vec{r})|^2.$$

The effective single-particle potential can be written in more detail as

$$V_s(\vec{r}) = V(\vec{r}) + \int \frac{e^2 n_s(\vec{r}')}{|\vec{r} - \vec{r}'|} d^3r' + V_{\text{XC}}[n_s(\vec{r})]$$

where the second term denotes the so-called Hartree term describing the electron-electron Coulomb repulsion, while the last term V_{XC} is called the exchange-correlation potential. Here, V_{XC} includes all the many-particle interactions. Since the Hartree term and V_{XC} depend on $n(\vec{r})$, which depends on the ϕ_i , which in turn depend on V_s , the problem of solving the Kohn-Sham equation has to be done in a self-consistent (i.e., iterative) way. Usually one starts with an initial guess for $n(\vec{r})$, then calculates the corresponding V_s and solves the Kohn-Sham equations for the ϕ_i . From these one calculates a new density and starts again. This procedure is then repeated until convergence is reached. A non-iterative approximate formulation called Harris functional DFT is an alternative approach to this.

Approximations (Exchange-correlation functionals)

The major problem with DFT is that the exact functionals for exchange and correlation are not known except for the free electron gas. However, approximations exist which permit the calculation of certain physical quantities quite accurately. In physics the most widely used approximation is the local-density approximation (LDA), where the functional depends only on the density at the coordinate where the functional is evaluated:

$$E_{XC}^{LDA}[n] = \int \epsilon_{XC}(n)n(\vec{r})d^3r.$$

The local spin-density approximation (LSDA) is a straightforward generalization of the LDA to include electron spin:

$$E_{XC}^{LSDA}[n_{\uparrow}, n_{\downarrow}] = \int \epsilon_{XC}(n_{\uparrow}, n_{\downarrow})n(\vec{r})d^3r.$$

Highly accurate formulae for the exchange-correlation energy density $\epsilon_{XC}(n_{\uparrow}, n_{\downarrow})$ have been constructed from quantum Monte Carlo simulations of a free electron model.^[14]

Generalized gradient approximations (GGA) are still local but also take into account the gradient of the density at the same coordinate:

$$E_{XC}^{GGA}[n_{\uparrow}, n_{\downarrow}] = \int \epsilon_{XC}(n_{\uparrow}, n_{\downarrow}, \vec{\nabla}n_{\uparrow}, \vec{\nabla}n_{\downarrow})n(\vec{r})d^3r.$$

Using the latter (GGA) very good results for molecular geometries and ground-state energies have been achieved.

Potentially more accurate than the GGA functionals are the meta-GGA functionals. These functionals include a further term in the expansion, depending on the density, the gradient of the density and the Laplacian (second derivative) of the density.

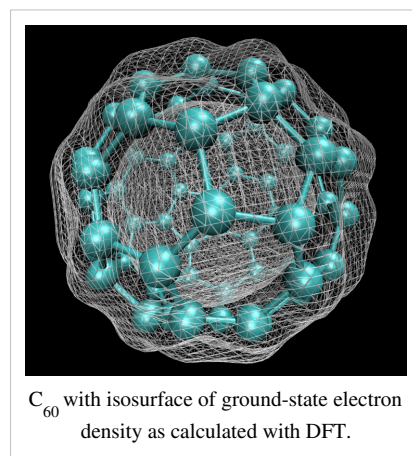
Difficulties in expressing the exchange part of the energy can be relieved by including a component of the exact exchange energy calculated from Hartree-Fock theory. Functionals of this type are known as hybrid functionals.

Generalizations to include magnetic fields

The DFT formalism described above breaks down, to various degrees, in the presence of a vector potential, i.e. a magnetic field. In such a situation, the one-to-one mapping between the ground-state electron density and wavefunction is lost. Generalizations to include the effects of magnetic fields have led to two different theories: current density functional theory (CDFT) and magnetic field functional theory (BDFT). In both these theories, the functional used for the exchange and correlation must be generalized to include more than just the electron density. In current density functional theory, developed by Vignale and Rasolt,^[9] the functionals become dependent on both the electron density and the paramagnetic current density. In magnetic field density functional theory, developed by Salsbury, Grayce and Harris, the functionals depend on the electron density and the magnetic field, and the functional form can depend on the form of the magnetic field. In both of these theories it has been difficult to develop functionals beyond their equivalent to LDA, which are also readily implementable computationally.

Applications

In practice, Kohn-Sham theory can be applied in several distinct ways depending on what is being investigated. In solid state calculations, the local density approximations are still commonly used along with plane wave basis sets, as an electron gas approach is more appropriate for electrons delocalised through an infinite solid. In molecular calculations, however, more sophisticated functionals are needed, and a huge variety of exchange-correlation functionals have been developed for chemical applications. Some of these are inconsistent with the uniform electron gas approximation, however, they must reduce to LDA in the electron gas limit. Among physicists, probably the most widely used functional is the revised Perdew-Burke-Ernzerhof exchange model (a direct generalized-gradient parametrization of the free electron gas with no free parameters); however, this is not sufficiently calorimetrically accurate for gas-phase molecular calculations. In the chemistry community, one popular functional is known as BLYP (from the name Becke for the exchange part and Lee, Yang and Parr for the correlation part). Even more widely used is B3LYP which is a hybrid functional in which the exchange energy, in this case from Becke's exchange functional, is combined with the exact energy from Hartree-Fock theory. Along with the component exchange and correlation functionals, three parameters define the hybrid functional, specifying how much of the exact exchange is mixed in. The adjustable parameters in hybrid functionals are generally fitted to a 'training set' of molecules. Unfortunately, although the results obtained with these functionals are usually sufficiently accurate for most applications, there is no systematic way of improving them (in contrast to some of the traditional wavefunction-based methods like configuration interaction or coupled cluster theory). Hence in the current DFT approach it is not possible to estimate the error of the calculations without comparing them to other methods or experiments.



For molecular applications, in particular for hybrid functionals, Kohn-Sham DFT methods are usually implemented just like Hartree-Fock itself.

Thomas–Fermi model

The predecessor to density functional theory was the **Thomas–Fermi model**, developed by Thomas and Fermi in 1927. They used a statistical model to approximate the distribution of electrons in an atom. The mathematical basis postulated that electrons are distributed uniformly in phase space with two electrons in every h^3 of volume.^[15] For each element of coordinate space volume d^3r we can fill out a sphere of momentum space up to the Fermi momentum p_f ^[16]

$$(4/3)\pi p_f^3(\vec{r}).$$

Equating the number of electrons in coordinate space to that in phase space gives:

$$n(\vec{r}) = \frac{8\pi}{3h^3} p_f^3(\vec{r}).$$

Solving for p_f and substituting into the classical kinetic energy formula then leads directly to a kinetic energy represented as a functional of the electron density:

$$t_{TF}[n] = \frac{p^2}{2m_e} \propto \frac{(n^{1/3})^2}{2m_e} \propto n^{2/3}(\vec{r})$$

$$T_{TF}[n] = C_F \int n(\vec{r}) n^{2/3}(\vec{r}) d^3r = C_F \int n^{5/3}(\vec{r}) d^3r$$

$$\text{where } C_F = \frac{3h^2}{10m_e} \left(\frac{3}{8\pi} \right)^{2/3}.$$

As such, they were able to calculate the energy of an atom using this kinetic energy functional combined with the classical expressions for the nuclear-electron and electron-electron interactions (which can both also be represented in terms of the electron density).

Although this was an important first step, the Thomas–Fermi equation's accuracy is limited because the resulting kinetic energy functional is only approximate, and because the method does not attempt to represent the exchange energy of an atom as a conclusion of the Pauli principle. An exchange energy functional was added by Dirac in 1928.

However, the Thomas–Fermi–Dirac theory remained rather inaccurate for most applications. The largest source of error was in the representation of the kinetic energy, followed by the errors in the exchange energy, and due to the complete neglect of electron correlation.

Teller (1962) showed that Thomas–Fermi theory cannot describe molecular bonding. This can be overcome by improving the kinetic energy functional.

The kinetic energy functional can be improved by adding the Weizsäcker (1935) correction.^{[17] [18]}

$$T_W[n] = \frac{1}{8} \frac{\hbar^2}{m} \int \frac{|\nabla n(\vec{r})|^2}{n(\vec{r})} d\vec{r}.$$

Hohenberg-Kohn Theorems

1. If two systems of electrons, one trapped in a potential $v_1(\vec{r})$ and the other in $v_2(\vec{r})$ have the same ground-state density $n(\vec{r})$ then necessarily $v_1(\vec{r}) - v_2(\vec{r}) = \text{const}$.

Corollary: the ground state density uniquely determines the potential and thus all properties of the system, including the many-body wave function. In particular, the "HK" functional, defined as $F[n] = T[n] + U[n]$ is a universal functional of the density (not depending explicitly on the external potential).

2. For any positive integer N and potential $v(\vec{r})$ the density functional $E_{(v,N)}[n] = F[n] + \int v(\vec{r})n(\vec{r})d^3r$ obtains its minimal value at the ground-state density of N electrons in the potential $v(\vec{r})$. The minimal value of $E_{(v,N)}[n]$ is then the ground state energy of this system.

Software supporting DFT

DFT is supported by many Quantum chemistry and solid state physics codes, often along with other methods.

See also

- Harris functional
- Basis set (chemistry)
- Gas in a box
- Helium atom
- Kohn–Sham equations
- Local density approximation
- Molecule
- Molecular design software
- Molecular modelling
- Quantum chemistry
- List of quantum chemistry and solid state physics software

- List of software for molecular mechanics modeling
- Thomas–Fermi model
- Time-dependent density functional theory

Books on DFT

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- [21] http://prola.aps.org/abstract/PR/v136/i3B/pB864_1
- [22] http://prola.aps.org/abstract/PR/v140/i4A/pA1133_1
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- [24] http://prola.aps.org/abstract/PRB/v37/i2/p785_1
- [25] <http://dx.doi.org/10.1063/1.1904586>
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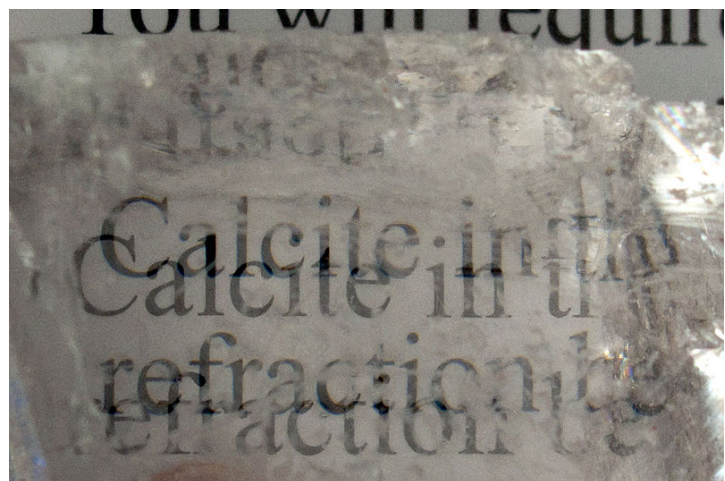
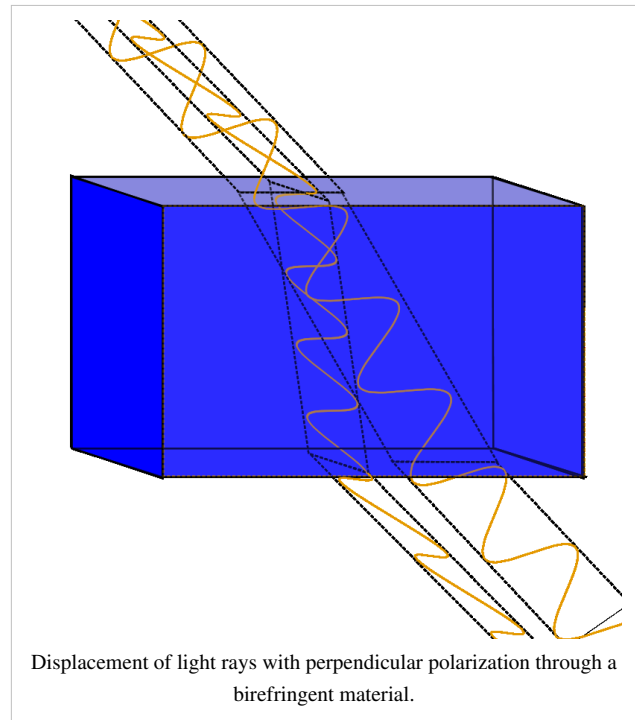
External links

- Walter Kohn, Nobel Laureate (<http://www.vega.org.uk/video/programme/23>) Freeview video interview with Walter on his work developing density functional theory by the Vega Science Trust.
- Klaus Capelle, A bird's-eye view of density-functional theory (<http://arxiv.org/abs/cond-mat/0211443>)
- Walter Kohn, Nobel Lecture (<http://nobelprize.org/chemistry/laureates/1998/kohn-lecture.pdf>)
- Density functional theory on arxiv.org (<http://xstructure.inr.ac.ru/x-bin/theme3.py?level=1&index1=447765>)
- FreeScience Library -> Density Functional Theory (<http://freescience.info/books.php?id=30>)
- Density Functional Theory -- an introduction (<http://arxiv.org/abs/physics/9806013>)
- Electron Density Functional Theory - Lecture Notes (http://www.fh.huji.ac.il/~roib/LectureNotes/DFT/DFT_Course_Roi_Baer.pdf)
- Density Functional Theory through Legendre Transformation (<http://ptp.ipap.jp/link?PTP/92/833/>)

Polarization Spectroscopy-Principles and Techniques

Birefringence

Birefringence, or **double refraction**, is the decomposition of a ray of light (and other electromagnetic radiation) into two rays (the **ordinary ray** and the **extraordinary ray**) when it passes through certain types of material, such as calcite crystals or boron nitride, depending on the polarization of the light. This effect can occur only if the structure of the material is anisotropic (directionally dependent). If the material has a single axis of anisotropy or optical axis (i.e. it is uniaxial), birefringence can be formalized by assigning two different refractive indices to the material for different polarizations. The birefringence magnitude is then defined by



A calcite crystal laid upon a paper with all letters showing the double refraction



A calcite crystal seen through a polarizing filter

$$\Delta n = n_e - n_o$$

where n_e and n_o are the refractive indices for polarizations parallel (**extraordinary**) and perpendicular (**ordinary**) to the axis of anisotropy respectively.^[1]

The reason for birefringence is the fact that in anisotropic media the electric field vector $\vec{E}$ and the dielectric displacement $\vec{D}$ can be nonparallel (namely for the extraordinary polarisation), although being linearly related.

Birefringence can also arise in magnetic, not dielectric, materials, but substantial variations in magnetic permeability of materials are rare at optical frequencies. Liquid crystal materials as used in Liquid Crystal Displays (LCDs) are also birefringent.^[2]

Creation

While birefringence is often found naturally (especially in crystals), there are several ways to create it in optically isotropic materials.

- Birefringence results when isotropic materials are deformed such that the isotropy is lost in one direction (i.e., stretched or bent). Example^[3]
- Applying an electric field can induce molecules to line up or behave asymmetrically, introducing anisotropy and resulting in birefringence. (*see* Pockels effect)
- Applying a magnetic field can cause a material to be **circularly birefringent**, with different indices of refraction for oppositely-handed circular polarizations
- Self alignment of highly polar molecules such as lipids and some surfactants will generate highly birefringent thin films (see also Liquid crystal)

Examples of uniaxial birefringent materials

Uniaxial materials, at 590 nm^[4]

Material	n_o	n_e	Δn
beryl $\text{Be}_3\text{Al}_2(\text{SiO}_3)_6$	1.602	1.557	-0.045
calcite CaCO_3	1.658	1.486	-0.172
calomel Hg_2Cl_2	1.973	2.656	+0.683
ice H_2O	1.309	1.313	+0.004
lithium niobate LiNbO_3	2.272	2.187	-0.085
magnesium fluoride MgF_2	1.380	1.385	+0.006
quartz SiO_2	1.544	1.553	+0.009
ruby Al_2O_3	1.770	1.762	-0.008
rutile TiO_2	2.616	2.903	+0.287
peridot $(\text{Mg, Fe})_2\text{SiO}_4$	1.690	1.654	-0.036
sapphire Al_2O_3	1.768	1.760	-0.008
sodium nitrate NaNO_3	1.587	1.336	-0.251
tourmaline (complex silicate)	1.669	1.638	-0.031
zircon, high ZrSiO_4	1.960	2.015	+0.055
zircon, low ZrSiO_4	1.920	1.967	+0.047

Many plastics are birefringent, because their molecules are 'frozen' in a stretched conformation when the plastic is moulded or extruded.^[5] For example, cellophane is a cheap birefringent material, and Polaroid sheets are commonly used to examine for orientation in birefringent plastics like polystyrene and polycarbonate. Birefringent materials are used in many devices which manipulate the polarization of light, such as wave plates, polarizing prisms, and Lyot filters.

There are many birefringent crystals: birefringence was first described in calcite crystals by the Danish scientist Rasmus Bartholin in 1669.^[6]

Birefringence can be observed in amyloid plaque deposits such as are found in the brains of Alzheimer's patients. Modified proteins such as immunoglobulin light chains abnormally accumulate between cells, forming fibrils. Multiple folds of these fibers line up and take on a beta-pleated sheet conformation. Congo red dye intercalates between the folds and, when observed under polarized light, causes birefringence.

Cotton (*Gossypium hirsutum*) fiber is birefringent because of high levels of cellulosic material in the fiber's secondary cell wall.

Slight imperfections in optical fiber can cause birefringence, which can cause distortion in fiber-optic communication; see polarization mode dispersion. The imperfections can be geometrically based, or a result of photoelastic effects from loading on the optical fiber.

Silicon carbide, also known as Moissanite, is strongly birefringent.

The refractive indices of several (uniaxial) birefringent materials are listed to the right (at wavelength ~ 590 nm)^[4]

Fast and slow rays

Effective refractive indices in uniaxial materials

Propagation direction	Ordinary ray		Extraordinary ray	
	Polarization	n_{eff}	Polarization	n_{eff}
z	xy -plane	n_o	n/a	n/a
xy -plane	xy -plane	n_o	z	n_e
xz -plane	y	n_o	xz -plane	$n_e < n < n_o$
other	analogous to xz -plane			

For a given propagation direction, there are generally two perpendicular polarizations for which the medium behaves as if it had a single effective refractive index. In a uniaxial material, rays with these polarizations are called the extraordinary and the ordinary ray (e and o rays), corresponding to the extraordinary and ordinary refractive indices. In a biaxial material, there are three refractive indices α , β , and γ , yet only two rays, which are called the fast and the slow ray. The slow ray is the ray that has the highest effective refractive index.

For a uniaxial material with the z axis defined to be the optical axis, the effective refractive indices are as in the table on the right. For rays propagating in the xz plane, the effective refractive index of the e polarization varies continuously between n_o and n_e , depending on the angle with the z axis. The effective refractive index can be constructed from the Index ellipsoid.

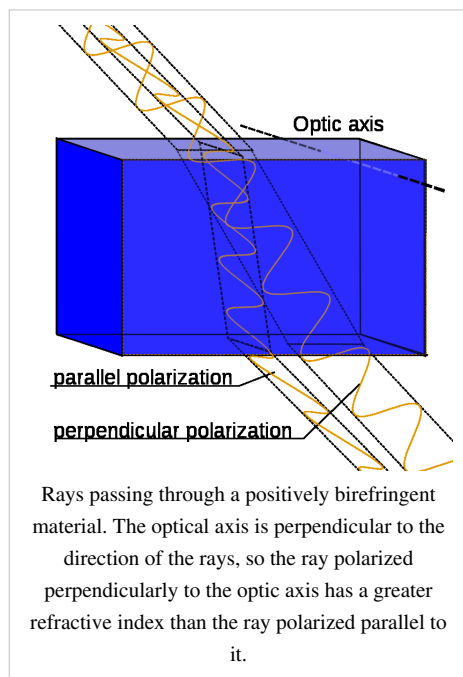
Biaxial birefringence

Biaxial materials, at 590 nm^[4]

Material	n_α	n_β	n_γ
borax	1.447	1.469	1.472
epsom salt $\text{MgSO}_4 \cdot 7(\text{H}_2\text{O})$	1.433	1.455	1.461
mica, biotite	1.595	1.640	1.640
mica, muscovite	1.563	1.596	1.601
olivine $(\text{Mg, Fe})_2\text{SiO}_4$	1.640	1.660	1.680
perovskite CaTiO_3	2.300	2.340	2.380
topaz	1.618	1.620	1.627
ulexite	1.490	1.510	1.520

Biaxial birefringence, also known as **trirefringence**, describes an anisotropic material that has more than one axis of anisotropy. For such a material, the refractive index tensor $\mathbf{n}$, will in general have three distinct eigenvalues that can be labeled n_α , n_β and n_γ .

Positive or negative



Uniaxial birefringent materials are classified as positively (or negatively) birefringent when, for light directed perpendicularly to the optic axis, the refractive index of light polarized parallel to the optic axis is greater (or smaller, respectively,) than light polarized perpendicularly to the optic axis.^[7] In other words, the polarization of the slow (or fast) wave is parallel to the optical axis when the birefringence of the crystal is positive (or negative, respectively).

Biaxial crystals are defined as positively (or negatively) birefringent when the slow ray (or fast ray, respectively) bisects the acute angle formed by the optical axes.^[8]

In practice, when using an optical compensator that emits red light, a crystal with positive birefringence appears blue when its long dimension is parallel to the slow axis of the compensator. In contrast, a crystal with negative birefringence appears yellow when its long dimension is parallel to the slow axis of the compensator, and the slow ray of the compensator is oriented perpendicularly to the long axis of the crystal.^[8] The reason for these phenomena is that the wavelength of

emitted light is shifted higher in positively birefringent crystals, because the slow ray of the crystal is parallel to the slow axis of the compensator,^[8] while for negatively birefringent crystals the wavelength of emitted light is shifted lower, because the fast ray of the crystal is parallel to the slow axis of the compensator.^[8] The order of colors resulting from the use of compensators in a polarized light system differs from that of a typical spectrum, instead having an order including yellow-orange-red-violet-blue.^[8]

Measurement

Birefringence and related optical effects (such as optical rotation and linear or circular dichroism) can be measured by measuring the changes in the polarization of light passing through the material. These measurements are known as polarimetry.

Birefringence of lipid bilayers can be measured using dual polarisation interferometry. This provides a measure of the degree of order within these fluid layers and how this order is disrupted when the layer interacts with other biomolecules.

A common feature of optical microscopes is a pair of crossed polarizing filters. Between the crossed polarizers, a birefringent sample will appear bright against a dark (isotropic) background.

For a fixed composition such as calcium carbonate, a crystal such as calcite or its polymorphs, the index of refraction depends on the direction of light through the crystal structure. The refraction also depends on composition, and can be calculated using the Gladstone-Dale relation.

Applications

Birefringence is widely used in optical devices, such as liquid crystal displays, light modulators, color filters, wave plates, optical axis gratings, etc. It also plays an important role in second harmonic generation and many other nonlinear processes.

It is also utilized in medical diagnostics. For example, needle aspiration of fluid from a gouty joint will reveal negatively birefringent

urate crystals. Calcium pyrophosphate crystals, in contrast, show weak positive birefringence.^[9] In ophthalmology, scanning laser polarimetry utilises the birefringence of the retinal nerve fibre layer to indirectly quantify its thickness, which is of use in the assessment and monitoring of glaucoma. Birefringence characteristics in sperm heads allow for the selection of spermatozoa for intracytoplasmic sperm injection.^[10] Likewise, *zona imaging* uses birefringence on oocytes to select the ones with highest chances of successful pregnancy.^[11] Birefringence of particles biopsied from pulmonary nodules indicates silicosis.

Birefringent filters are also used as spatial low-pass filters in electronic cameras, where the thickness of the crystal is controlled to spread the image in one direction, thus increasing the spot-size. This is essential to the proper working of all television and electronic film cameras, to avoid spatial aliasing, the folding back of frequencies higher than can be sustained by the pixel matrix of the camera.



A calcite crystal laid upon a paper with some letters showing the double refraction

Elastic birefringence

Another form of birefringence is observed in anisotropic elastic materials. In these materials, shear waves split according to similar principles as the light waves discussed above. The study of birefringent shear waves in the earth is a part of seismology. Birefringence is also used in optical mineralogy to determine the chemical composition, and history of minerals and rocks.

Stress induced birefringence



Color pattern of a plastic box with 'frozen' in mechanical stress placed between two crossed polarizers.

Isotropic solids do not exhibit birefringence. However, when they are under mechanical stress, birefringence results. The stress can be applied externally or is 'frozen' in after a birefringent plastic ware is cooled after it is manufactured using injection molding. When such a sample is placed between two crossed polarizers, colour patterns can be observed due to stress induced birefringence. The reason is that polarization of a light ray is usually rotated after passing through a birefringent material and the amount of rotation is dependent on wavelength.

Mathematical description

More generally, birefringence can be defined by considering a dielectric permittivity and a refractive index that are tensors. Consider a plane wave propagating in an anisotropic medium, with a relative permittivity tensor ϵ , where the refractive index $\mathbf{n}$, is defined by $\mathbf{n} \cdot \mathbf{n} = \epsilon$. If the wave has an electric vector of the form:

$$\mathbf{E} = \mathbf{E}_0 \exp i(\mathbf{k} \cdot \mathbf{r} - \omega t) \quad (2)$$

where $\mathbf{r}$ is the position vector and t is time, then the wave vector $\mathbf{k}$ and the angular frequency ω must satisfy Maxwell's equations in the medium, leading to the equations:

$$-\nabla \times \nabla \times \mathbf{E} = \frac{1}{c^2} (\epsilon \cdot \frac{\partial^2 \mathbf{E}}{\partial t^2}) \quad (3a)$$

$$\nabla \cdot (\epsilon \cdot \mathbf{E}) = 0 \quad (3b)$$

where c is the speed of light in a vacuum. Substituting eqn. 2 in eqns. 3a-b leads to the conditions:

$$|\mathbf{k}|^2 \mathbf{E}_0 - (\mathbf{k} \cdot \mathbf{E}_0) \mathbf{k} = \frac{\omega^2}{c^2} (\epsilon \cdot \mathbf{E}_0) \quad (4a)$$

$$\mathbf{k} \cdot (\epsilon \cdot \mathbf{E}_0) = 0 \quad (4b)$$

For the matrix product $(\epsilon \cdot \mathbf{E})$ often a separate name is used, the *dielectric displacement vector* $\mathbf{D}$. So essentially birefringence concerns the general theory of linear relationships between these two vectors in anisotropic media. To find the allowed values of $\mathbf{k}$, $\mathbf{E}_0$ can be eliminated from eq 4a. One way to do this is to write eqn 4a in Cartesian coordinates, where the x , y and z axes are chosen in the directions of the eigenvectors of ϵ , so that

$$\epsilon = \begin{bmatrix} n_x^2 & 0 & 0 \\ 0 & n_y^2 & 0 \\ 0 & 0 & n_z^2 \end{bmatrix} \quad (4c)$$

Hence eqn 4a becomes

$$(-k_y^2 - k_z^2 + \frac{\omega^2 n_x^2}{c^2}) E_x + k_x k_y E_y + k_x k_z E_z = 0 \quad (5a)$$

$$k_x k_y E_x + (-k_x^2 - k_z^2 + \frac{\omega^2 n_y^2}{c^2}) E_y + k_y k_z E_z = 0 \quad (5b)$$

$$k_x k_z E_x + k_y k_z E_y + (-k_x^2 - k_y^2 + \frac{\omega^2 n_z^2}{c^2}) E_z = 0 \quad (5c)$$

where E_x, E_y, E_z, k_x, k_y and k_z are the components of $\mathbf{E}_0$ and $\mathbf{k}$. This is a set of linear equations in E_x, E_y, E_z , and they have a non-trivial solution if their determinant is zero:

$$\det \begin{bmatrix} (-k_y^2 - k_z^2 + \frac{\omega^2 n_x^2}{c^2}) & k_x k_y & k_x k_z \\ k_x k_y & (-k_x^2 - k_z^2 + \frac{\omega^2 n_y^2}{c^2}) & k_y k_z \\ k_x k_z & k_y k_z & (-k_x^2 - k_y^2 + \frac{\omega^2 n_z^2}{c^2}) \end{bmatrix} = 0 \quad (6)$$

Multiplying out eqn (6), and rearranging the terms, we obtain

$$\frac{\omega^4}{c^4} - \frac{\omega^2}{c^2} \left(\frac{k_x^2 + k_y^2}{n_z^2} + \frac{k_x^2 + k_z^2}{n_y^2} + \frac{k_y^2 + k_z^2}{n_x^2} \right) + \left(\frac{k_x^2}{n_y^2 n_z^2} + \frac{k_y^2}{n_x^2 n_z^2} + \frac{k_z^2}{n_x^2 n_y^2} \right) (k_x^2 + k_y^2 + k_z^2) = 0 \quad (7)$$

In the case of a uniaxial material, where $n_x = n_y = n_o$ and $n_z = n_e$ say, eqn 7 can be factorised into

$$\left(\frac{k_x^2}{n_o^2} + \frac{k_y^2}{n_o^2} + \frac{k_z^2}{n_o^2} - \frac{\omega^2}{c^2} \right) \left(\frac{k_x^2}{n_e^2} + \frac{k_y^2}{n_e^2} + \frac{k_z^2}{n_o^2} - \frac{\omega^2}{c^2} \right) = 0 \quad (8)$$

Each of the factors in eqn 8 defines a surface in the space of vectors $\mathbf{k}$ — the **surface of wave normals**. The first factor defines a sphere and the second defines an ellipsoid. Therefore, for each direction of the wave normal, two wavevectors $\mathbf{k}$ are allowed. Values of $\mathbf{k}$ on the sphere correspond to the **ordinary rays** while values on the ellipsoid

correspond to the **extraordinary rays**.

For a biaxial material, eqn (7) cannot be factorized in the same way, and describes a more complicated pair of wave-normal surfaces.^[12]

Birefringence is often measured for rays propagating along one of the optical axes (or measured in a two-dimensional material). In this case, $\mathbf{n}$ has two eigenvalues which can be labeled n_1 and n_2 . $\mathbf{n}$ can be diagonalized by:

$$\mathbf{n} = \mathbf{R}(\chi) \cdot \begin{bmatrix} n_1 & 0 \\ 0 & n_2 \end{bmatrix} \cdot \mathbf{R}(\chi)^T \quad (9)$$

where $\mathbf{R}(\chi)$ is the rotation matrix through an angle χ . Rather than specifying the complete tensor $\mathbf{n}$, we may now simply specify the *magnitude* of the birefringence Δn , and *extinction angle* χ , where $\Delta n = n_1 - n_2$.

See also

- Cotton-Mouton effect
- Crystal optics
- John Kerr
- Periodic poling
- Dichroism

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External links

- <http://www.olympusmicro.com/primer/lightandcolor/birefringence.html>
- (<http://www.youtube.com/watch?v=BEClYQbuG7U>) Video of stress birefringence in Polymethylmethacrylate (PMMA or Plexiglas).
- Application note on the theory of birefringence (http://www.campoly.com/application_notes.html) (see no.14)

Polarization spectroscopy

Polarization spectroscopy comprises a set of spectroscopic techniques based on polarization properties of light (not necessarily visible one; UV, X-ray, infrared, or in any other frequency range of the electromagnetic radiation). By analyzing the polarization properties of light, decisions can be made about the media that emitted the light (or the media the light passes/scatters through). Alternatively, a source of polarized light may be used to probe a media; in this case, the changes in the light polarization (comparing to the incidental one) allow to infer the media properties.

In general, any kind of anisotropy in the media results in some sort of light polarization. Such an anisotropy can be either inherent to the media (e.g., in the case of a crystal substance), or imposed externally (e.g., in the presence of magnetic field in plasma).

Polarized IR Spectroscopy

Infrared spectroscopy (IR spectroscopy) is the spectroscopy that deals with the infrared region of the electromagnetic spectrum, that is light with a longer wavelength and lower frequency than visible light. It covers a range of techniques, mostly based on absorption spectroscopy. As with all spectroscopic techniques, it can be used to identify and study chemicals. A common laboratory instrument that uses this technique is a Fourier transform infrared (FTIR) spectrometer.

The infrared portion of the electromagnetic spectrum is usually divided into three regions; the near-, mid- and far-infrared, named for their relation to the visible spectrum. The higher energy near-IR, approximately $14000\text{--}4000\text{ cm}^{-1}$ ($0.8\text{--}2.5\text{ }\mu\text{m}$ wavelength) can excite overtone or harmonic vibrations. The mid-infrared, approximately $4000\text{--}400\text{ cm}^{-1}$ ($2.5\text{--}25\text{ }\mu\text{m}$) may be used to study the fundamental vibrations and associated rotational-vibrational structure. The far-infrared, approximately $400\text{--}10\text{ cm}^{-1}$ ($25\text{--}1000\text{ }\mu\text{m}$), lying adjacent to the microwave region, has low energy and may be used for rotational spectroscopy. The names and classifications of these subregions are conventions, and are only loosely based on the relative molecular or electromagnetic properties.

Theory

Infrared spectroscopy exploits the fact that molecules absorb specific frequencies that are characteristic of their structure. These absorptions are resonant frequencies, i.e. the frequency of the absorbed radiation matches the frequency of the bond or group that vibrates. The energies are determined by the shape of the molecular potential energy surfaces, the masses of the atoms, and the associated vibronic coupling.

In particular, in the Born–Oppenheimer and harmonic approximations, i.e. when the molecular Hamiltonian corresponding to the electronic ground state can be approximated by a harmonic oscillator in the neighborhood of the equilibrium molecular geometry, the resonant frequencies are determined by the normal modes corresponding to the molecular electronic ground state potential energy surface. Nevertheless, the resonant frequencies can be in a first approach related to the strength of the bond, and the mass of the atoms at either end of it. Thus, the frequency of the vibrations can be associated with a particular bond type.

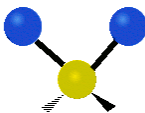
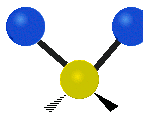
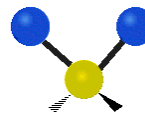
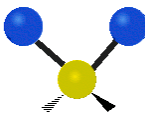
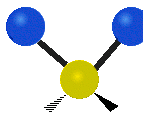
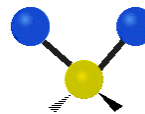
Number of vibrational modes

In order for a vibrational mode in a molecule to be "IR active," it must be associated with changes in the permanent dipole.

A molecule can vibrate in many ways, and each way is called a *vibrational mode*. Linear molecules have $3N - 5$ degrees of vibrational modes whereas nonlinear molecules have $3N - 6$ degrees of vibrational modes (also called vibrational degrees of freedom). As an example H_2O , a non-linear molecule, will have $3 \times 3 - 6 = 3$ degrees of vibrational freedom, or modes.

Simple diatomic molecules have only one bond and only one vibrational band. If the molecule is symmetrical, e.g. N_2 , the band is not observed in the IR spectrum, but only in the Raman spectrum. Unsymmetrical diatomic molecules, e.g. CO, absorb in the IR spectrum. More complex molecules have many bonds, and their vibrational spectra are correspondingly more complex, i.e. big molecules have many peaks in their IR spectra.

The atoms in a CH_2 group, commonly found in organic compounds, can vibrate in six different ways: **symmetric and antisymmetric stretching, scissoring, rocking, wagging and twisting**:

Symmetrical stretching	Antisymmetrical stretching	Scissoring
		
Rocking	Wagging	Twisting
		

(These figures do not represent the "recoil" of the C atoms, which, though necessarily present to balance the overall movements of the molecule, are much smaller than the movements of the lighter H atoms).

Special effects

The simplest and most important IR bands arise from the "normal modes," the simplest distortions of the molecule. In some cases, "overtone bands" are observed. These bands arise from the absorption of a photon that leads to a doubly excited vibrational state. Such bands appear at approximately twice the energy of the normal mode. Some vibrations, so-called 'combination modes,' involve more than one normal mode. The phenomenon of Fermi resonance can arise when two modes are similar in energy, Fermi resonance results in an unexpected shift in energy and intensity of the bands.

Practical IR spectroscopy

The infrared spectrum of a sample is recorded by passing a beam of infrared light through the sample. Examination of the transmitted light reveals how much energy was absorbed at each wavelength. This can be done with a monochromatic beam, which changes in wavelength over time, or by using a Fourier transform instrument to measure all wavelengths at once. From this, a transmittance or absorbance spectrum can be produced, showing at which IR wavelengths the sample absorbs. Analysis of these absorption characteristics reveals details about the molecular structure of the sample. When the frequency of the IR is the same as the vibrational frequency of a bond, absorption occurs.

This technique works almost exclusively on samples with covalent bonds. Simple spectra are obtained from samples with few IR active bonds and high levels of purity. More complex molecular structures lead to more absorption bands and more complex spectra. The technique has been used for the characterization of very complex mixtures.

Sample preparation

Gaseous samples require a sample cell with a long pathlength (typically 5–10 cm), to compensate for the diluteness.

Liquid samples can be sandwiched between two plates of a salt (commonly sodium chloride, or common salt, although a number of other salts such as potassium bromide or calcium fluoride are also used).^[1] The plates are transparent to the infrared light and do not introduce any lines onto the spectra.

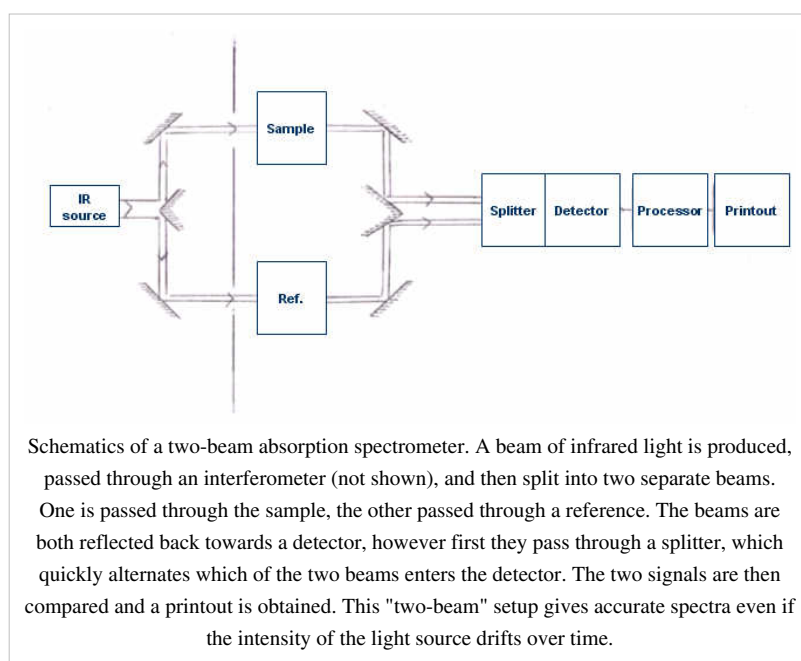
Solid samples can be prepared in a variety of ways. One common method is to crush the sample with an oily mulling agent (usually Nujol) in a marble or agate mortar, with a pestle. A thin film of the mull is smeared onto salt plates and measured. The second method is to grind a quantity of the sample with a specially purified salt (usually potassium bromide) finely (to remove scattering effects from large crystals). This powder mixture is then pressed in a mechanical press to form a translucent pellet through which the beam of the spectrometer can pass.^[1] A third technique is the "cast film" technique, which is used mainly for polymeric materials. The sample is first dissolved in a suitable, non hygroscopic solvent. A drop of this solution is deposited on surface of KBr or NaCl cell. The solution is then evaporated to dryness and the film formed on the cell is analysed directly. Care is important to ensure that the film is not too thick otherwise light cannot pass through. This technique is suitable for qualitative analysis. The final method is to use microtomy to cut a thin (20–100 μm) film from a solid sample. This is one of the most important ways of analysing failed plastic products for example because the integrity of the solid is preserved.

It is important to note that spectra obtained from different sample preparation methods will look slightly different from each other due to differences in the samples' physical states.

Comparing to a reference

To take the infrared spectrum of a sample, it is necessary to measure both the sample and a "reference" (or "control"). This is because each measurement is affected by not only the light-absorption properties of the sample, but also the properties of the instrument (for example, what light source is used, what detector is used, etc.). The reference measurement makes it possible to eliminate the instrument influence. Mathematically, the sample transmission spectrum is divided by the reference transmission spectrum.

The appropriate "reference" depends on the measurement and its goal. The simplest reference measurement is to simply remove the sample (replacing it by air). However, sometimes a different reference is more useful. For example, if the sample is a dilute solute dissolved in water in a beaker, then a good reference measurement might be to measure pure water in the same beaker. Then the reference measurement would cancel out not only all the instrumental properties (like what light source is used), but also the light-absorbing and light-reflecting properties of the water and beaker, and the final result would just show the properties of the solute (at



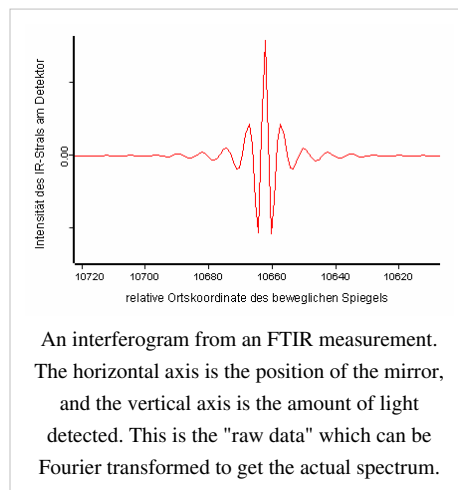
least approximately).

A common way to compare to a reference is sequentially: First measure the reference, then replace the reference by the sample, then measure the sample. This technique is not perfectly reliable: If the infrared lamp is a bit brighter during the reference measurement, then a bit dimmer during the sample measurement, the measurement will be distorted. More elaborate methods, such as a "two-beam" setup (see figure), can correct for these types of effects to give very accurate results.

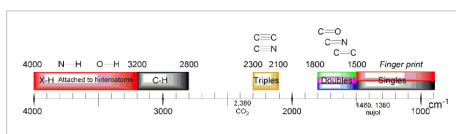
FTIR

Fourier transform infrared (FTIR) spectroscopy is a measurement technique that allows one to record infrared spectra. Infrared light is guided through an interferometer and then through the sample (or vice versa). A moving mirror inside the apparatus alters the distribution of infrared light that passes through the interferometer. The signal directly recorded, called an "interferogram", represents light output as a function of mirror position. A data-processing technique called Fourier transform turns this raw data into the desired result (the sample's spectrum): Light output as a function of infrared wavelength (or equivalently, wavenumber). As described above, the sample's spectrum is always compared to a reference.

There is an alternate method for taking spectra (the "dispersive" or "scanning monochromator" method), where one wavelength at a time passes through the sample. The dispersive method is more common in UV-Vis spectroscopy, but is less practical in the infrared than the FTIR method. One reason that FTIR is favored is called " Fellgett's advantage" or the "multiplex advantage": The information at all frequencies is collected simultaneously, improving both speed and signal-to-noise ratio. Another is called "Jacquinot's Throughput Advantage": A dispersive measurement requires detecting much lower light levels than an FTIR measurement.^[2] There are other advantages, as well as some disadvantages,^[2] but virtually all modern infrared spectrometers are FTIR instruments.



Absorption bands



Wavenumbers listed in cm⁻¹.

Uses and applications

Infrared spectroscopy is widely used in both research and industry as a simple and reliable technique for measurement, quality control and dynamic measurement. It is also used in forensic analysis in both criminal and civil cases, enabling identification of polymer degradation for example.

The instruments are now small, and can be transported, even for use in field trials. With increasing technology in computer filtering and manipulation of the results, samples in solution can now be measured accurately (water produces a broad absorbance across the range of interest, and thus renders the spectra unreadable without this computer treatment). Some instruments will also automatically tell you what substance is being measured from a store of thousands of reference spectra held in storage.

By measuring at a specific frequency over time, changes in the character or quantity of a particular bond can be measured. This is especially useful in measuring the degree of polymerization in polymer manufacture. Modern research instruments can take infrared measurements across the whole range of interest as frequently as 32 times a second. This can be done whilst simultaneous measurements are made using other techniques. This makes the observations of chemical reactions and processes quicker and more accurate.

Infrared spectroscopy has been highly successful for applications in both organic and inorganic chemistry. Infrared spectroscopy has also been successfully utilized in the field of semiconductor microelectronics.^[3] for example, infrared spectroscopy can be applied to semiconductors like silicon, gallium arsenide, gallium nitride, zinc selenide, amorphous silicon, silicon nitride, etc.

Isotope effects

The different isotopes in a particular species may give fine detail in infrared spectroscopy. For example, the O–O stretching frequency (in reciprocal centimeters) of oxyhemocyanin is experimentally determined to be 832 and 788 cm⁻¹ for $\nu(^{16}\text{O}-^{16}\text{O})$ and $\nu(^{18}\text{O}-^{18}\text{O})$, respectively.

By considering the O–O bond as a spring, the wavenumber of absorbance, ν can be calculated:

$$\nu = \frac{1}{2\pi c} \sqrt{\frac{k}{\mu}}$$

where k is the spring constant for the bond, c is the speed of light, and μ is the reduced mass of the A–B system:

$$\mu = \frac{m_A m_B}{m_A + m_B}$$

(m_i is the mass of atom i).

The reduced masses for $^{16}\text{O}-^{16}\text{O}$ and $^{18}\text{O}-^{18}\text{O}$ can be approximated as 8 and 9 respectively. Thus

$$\frac{\nu(^{16}\text{O})}{\nu(^{18}\text{O})} = \sqrt{\frac{9}{8}} \approx \frac{832}{788}.$$

Where ν is the wavenumber; [wavenumber = frequency/(speed of light)]

The effect of isotopes, both on the vibration and the decay dynamics, has been found to be stronger than previously thought. In some systems, such as silicon and germanium, the decay of the anti-symmetric stretch mode of interstitial oxygen involves the symmetric stretch mode with a strong isotope dependence. For example, it was shown that for a natural silicon sample, the lifetime of the anti-symmetric vibration is 11.4 ps. When the isotope of one of the silicon atoms is increased to ^{29}Si , the lifetime increases to 19 ps. In similar manner, when the silicon atom is changed to ^{30}Si , the lifetime becomes 27 ps.^[4]

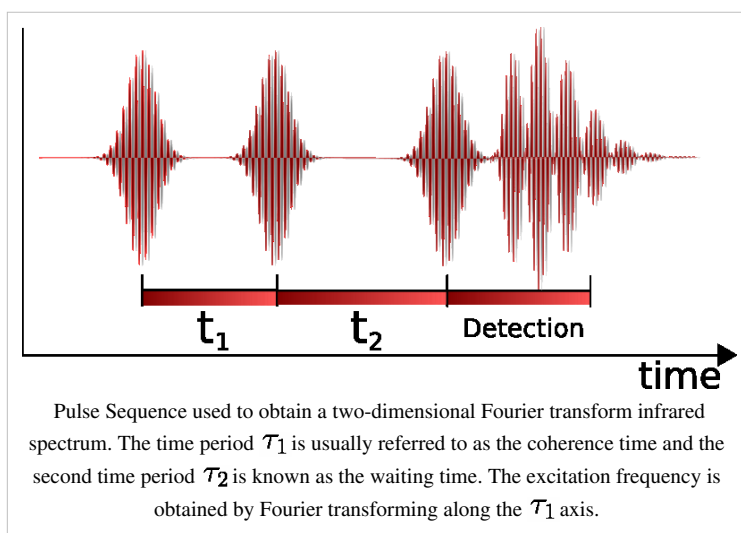
Two-dimensional IR

Two-dimensional infrared correlation spectroscopy analysis is the application of 2D correlation analysis on infrared spectra. By extending the spectral information of a perturbed sample, spectral analysis is simplified and resolution is enhanced. The 2D synchronous and 2D asynchronous spectra represent a graphical overview of the spectral changes due to a perturbation (such as a changing concentration or changing temperature) as well as the relationship between the spectral changes at two different wavenumbers.

Nonlinear two-dimensional infrared spectroscopy^{[5] [6]}

is the infrared version of correlation spectroscopy. Nonlinear two-dimensional infrared spectroscopy is a technique that has become available with the development of femtosecond infrared laser pulses. In this experiment, first a set of pump pulses are applied to the sample. This is followed by a waiting time, wherein the system is allowed to relax. The typical waiting time lasts from zero to several picoseconds, and the duration can be controlled with a resolution of tens of femtoseconds. A probe pulse is then applied

resulting in the emission of a signal from the sample. The nonlinear two-dimensional infrared spectrum is a two-dimensional correlation plot of the frequency ω_1 that was excited by the initial pump pulses and the frequency ω_3 excited by the probe pulse after the waiting time. This allows the observation of coupling between different vibrational modes; because of its extremely high time resolution, it can be used to monitor molecular dynamics on a picosecond timescale. It is still a largely unexplored technique and is becoming increasingly popular for fundamental research.



As with two-dimensional nuclear magnetic resonance (2DNMR) spectroscopy, this technique spreads the spectrum in two dimensions and allows for the observation of cross peaks that contain information on the coupling between different modes. In contrast to 2DNMR, nonlinear two-dimensional infrared spectroscopy also involves the excitation to overtones. These excitations result in excited state absorption peaks located below the diagonal and cross peaks. In 2DNMR, two distinct techniques, COSY and NOESY, are frequently used. The cross peaks in the first are related to the scalar coupling, while in the later they are related to the spin transfer between different nuclei. In nonlinear two-dimensional infrared spectroscopy, analogs have been drawn to these 2DNMR techniques. Nonlinear two-dimensional infrared spectroscopy with zero waiting time corresponds to COSY, and nonlinear two-dimensional infrared spectroscopy with finite waiting time allowing vibrational population transfer corresponds to NOESY. The COSY variant of nonlinear two-dimensional infrared spectroscopy has been used for determination of the secondary structure content proteins.^[7]

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External links

- A useful gif animation of different vibrational modes: SHU.ac.uk (<http://www.shu.ac.uk/schools/sci/chem/tutorials/molspec/irspec1.htm>)
- Infrared spectroscopy for organic chemists (<http://www.dq.fct.unl.pt/qoa/jas/ir.html>)
- Organic compounds spectrum database (http://riodb01.ibase.aist.go.jp/sdbs/cgi-bin/cre_index.cgi?lang=eng)

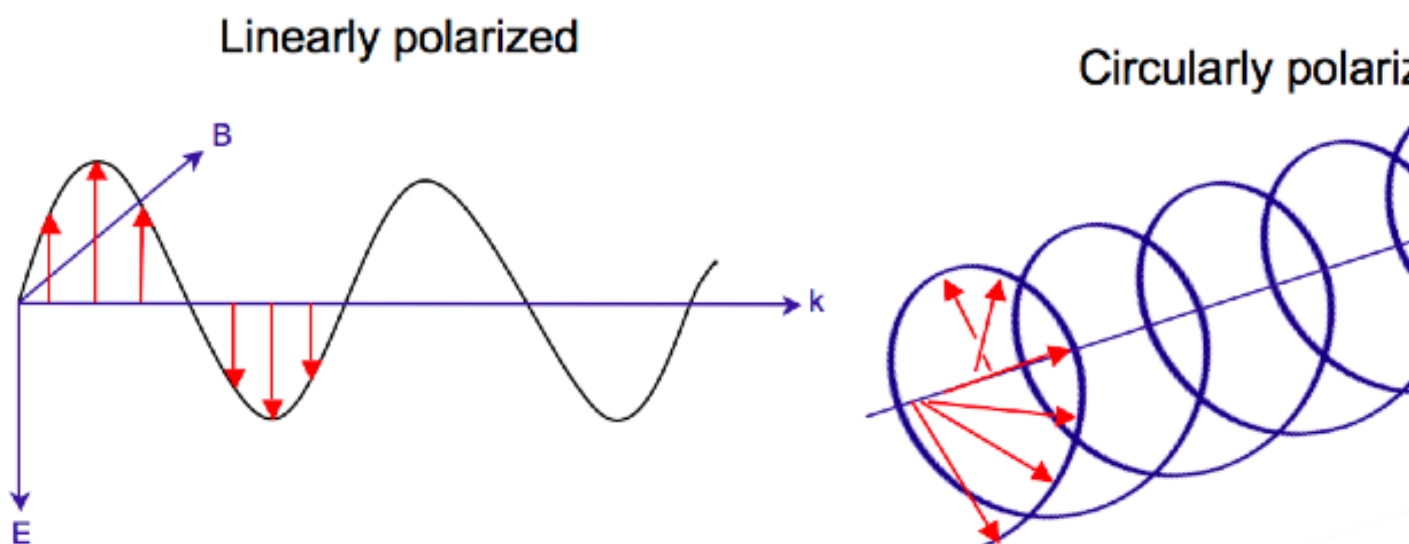
Circular dichroism

First pioneered by Jean-Baptiste Biot, Augustin Fresnel, and Aimé Cotton^[1], **circular dichroism (CD)** refers to the differential absorption of left and right circularly polarized light.^{[2] [3]} This phenomenon is exhibited in the absorption bands of optically active chiral molecules. CD spectroscopy has a wide range of applications in many different fields. Most notably, UV CD is used to investigate the secondary structure of proteins^[4]. UV/Vis CD is used to investigate charge-transfer transitions^[5]. Near-infrared CD is used to investigate geometric and electronic structure by probing metal d→d transitions^[6]. Vibrational circular dichroism, which uses light from the infrared energy region, is used for structural studies of small organic molecules, and most recently proteins and DNA^[7].

Physical Principles

Circular polarization of light

Electromagnetic radiation consists of an electric and magnetic field that oscillate perpendicular to one another and to the propagating direction^[8]. While linearly polarized light occurs when the electric field vector oscillates only in one plane and changes in magnitude, circularly polarized light occurs when the electric field vector rotates about its propagation direction and retains constant magnitude. Hence, it forms a helix in space while propagating. For left circularly polarized light (LCP) with propagation towards the observer, the electric vector rotates counterclockwise^[9]. For right circularly polarized light (RCP), the electric vector rotates clockwise.



Interaction of circularly polarized light with matter

When circularly polarized light passes through an absorbing optically active medium, the speeds between right and left polarizations differ ($c_L \neq c_R$) as well as their wavelength ($\lambda_L \neq \lambda_R$) and the extent to which they are absorbed ($\epsilon_L \neq \epsilon_R$). *Circular dichroism* is the difference $\Delta\epsilon \equiv \epsilon_L - \epsilon_R$ ^[10]. The electric field of a light beam causes a linear displacement of charge when interacting with a molecule (electric dipole), whereas the magnetic field of it causes a circulation of charge (magnetic dipole). These two motions combined cause an excitation of an electron in a helical motion, which includes translation and rotation and their associated operators. The experimentally determined relationship between the rotational strength (R) of a sample and the $\Delta\epsilon$ is given by

$$R_{exp} = \frac{3hc10^3 \ln(10)}{32\pi^3 N_A} \int \frac{\Delta\epsilon}{\nu} d\nu$$

The rotational strength has also been determined theoretically,

$$R_{theo} = \frac{1}{2mc} Im \int \Psi_g \widehat{M}_{(elec.dipole)} \Psi_e d\tau \bullet \int \Psi_g \widehat{M}_{(mag.dipole)} \Psi_e d\tau$$

We see from these two equations that in order to have non-zero $\Delta\epsilon$, the electric and magnetic dipole moment operators ($\widehat{M}_{(elec.dipole)}$ and $\widehat{M}_{(mag.dipole)}$) must transform as the same irreducible representation. C_n and D_n are the only point groups where this can occur, making only chiral molecules CD active.

Simply put, since circularly polarized light itself is "chiral", it interacts differently with chiral molecules. That is, the two types of circularly polarized light are absorbed to different extents. In a CD experiment, equal amounts of left and right circularly polarized light of a selected wavelength are alternately radiated into a (chiral) sample. One of the two polarizations is absorbed more than the other one, and this wavelength-dependent difference of absorption is measured, yielding the CD spectrum of the sample. Due to the interaction with the molecule, the electric field vector of the light traces out an elliptical path after passing through the sample.

Delta absorbance

By definition,

$$\Delta A = A_L - A_R$$

where ΔA (Delta Absorbance) is the difference between absorbance of left circularly polarized (LCP) and right circularly polarized (RCP) light (this is what is usually measured). ΔA is a function of wavelength, so for a measurement to be meaningful the wavelength at which it was performed must be known.

Molar circular dichroism

It can also be expressed, by applying Beer's law, as:

$$\Delta A = (\epsilon_L - \epsilon_R)Cl$$

where

ϵ_L and ϵ_R are the molar extinction coefficients for LCP and RCP light,

C is the molar concentration

l is the path length in centimeters (cm).

Then

$$\Delta\epsilon = \epsilon_L - \epsilon_R$$

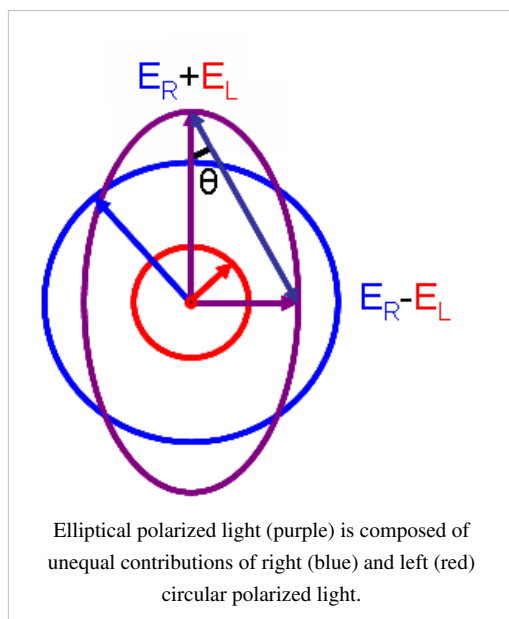
is the molar circular dichroism. This intrinsic property is what is usually meant by the circular dichroism of the substance. Since $\Delta\epsilon$ is a function of wavelength, a molar circular dichroism value ($\Delta\epsilon$) must specify the wavelength at which it is valid.

Extrinsic effects on circular dichroism

In many practical applications of circular dichroism (CD), as discussed below, the measured CD is not simply an intrinsic property of the molecule, but rather depends on the molecular conformation. In such a case the CD may also be a function of temperature, concentration, and the chemical environment, including solvents. In this case the reported CD value must also specify these other relevant factors in order to be meaningful.

Molar ellipticity

Although ΔA is usually measured, for historical reasons most measurements are reported in degrees of ellipticity. Molar circular dichroism and molar ellipticity, $[\theta]$, are readily interconverted by the equation:



$$[\theta] = 3298.2 \Delta \epsilon.$$

This relationship is derived by defining the ellipticity of the polarization as:

$$\tan \theta = \frac{E_R - E_L}{E_R + E_L}$$

where

E_R and E_L are the magnitudes of the electric field vectors of the right-circularly and left-circularly polarized light, respectively.

When E_R equals E_L (when there is no difference in the absorbance of right- and left-circular polarized light), θ is 0° and the light is linearly polarized. When either E_R or E_L is equal to zero (when there is complete absorbance of the circular polarized light in one direction), θ is 45° and the light is circularly polarized.

Generally, the circular dichroism effect is small, so $\tan \theta$ is small and can be approximated as θ in radians. Since the intensity or irradiance, I , of light is proportional to the square of the electric-field vector, the ellipticity becomes:

$$\theta(\text{radians}) = \frac{(I_R^{1/2} - I_L^{1/2})}{(I_R^{1/2} + I_L^{1/2})}$$

Then by substituting for I using Beer's law in natural logarithm form:

$$I = I_0 e^{-A \ln 10}$$

The ellipticity can now be written as:

$$\theta(\text{radians}) = \frac{(e^{\frac{-A_R}{2} \ln 10} - e^{\frac{-A_L}{2} \ln 10})}{(e^{\frac{-A_R}{2} \ln 10} + e^{\frac{-A_L}{2} \ln 10})} = \frac{e^{\Delta A \frac{\ln 10}{2}} - 1}{e^{\Delta A \frac{\ln 10}{2}} + 1}$$

Since $\Delta A \ll 1$, this expression can be approximated by expanding the exponentials in a Taylor series to first-order and then discarding terms of ΔA in comparison with unity and converting from radians to degrees:

$$\theta(\text{degrees}) = \Delta A \left(\frac{\ln 10}{4} \right) \left(\frac{180}{\pi} \right)$$

The linear dependence of solute concentration and pathlength is removed by defining molar ellipticity as,

$$[\theta] = \frac{100\theta}{Cl}$$

Then combining the last two expression with Beer's law, molar ellipticity becomes:

$$[\theta] = 100 \Delta \epsilon \left(\frac{\ln 10}{4} \right) \left(\frac{180}{\pi} \right) = 3298.2 \Delta \epsilon$$

Mean residue ellipticity

Methods for estimating secondary structure in polymers, proteins and polypeptides in particular, often require that the measured molar ellipticity spectrum be converted to a normalized value, specifically a value independent of the polymer length. Mean residue ellipticity is used for this purpose; it is simply the measured molar ellipticity of the molecule divided by the number of monomer units (residues) in the molecule.

Application to biological molecules

In general, this phenomenon will be exhibited in absorption bands of any optically active molecule. As a consequence, circular dichroism is exhibited by biological molecules, because of their dextrorotary and levorotary components. Even more important is that a secondary structure will also impart a distinct CD to its respective molecules. Therefore, the alpha helix of proteins and the double helix of nucleic acids have CD spectral signatures representative of their structures. The capacity of CD to give a representative structural signature makes it a powerful tool in modern biochemistry with applications that can be found in virtually every field of study.

CD is closely related to the optical rotatory dispersion (ORD) technique, and is generally considered to be more advanced. CD is measured in or near the absorption bands of the molecule of interest, while ORD can be measured far from these bands. CD's advantage is apparent in the data analysis. Structural elements are more clearly distinguished since their recorded bands do not overlap extensively at particular wavelengths as they do in ORD. In principle these two spectral measurements can be interconverted through an integral transform (Kramers–Kronig relation), if all the absorptions are included in the measurements.

The far-UV (ultraviolet) CD spectrum of proteins can reveal important characteristics of their secondary structure. CD spectra can be readily used to estimate the fraction of a molecule that is in the alpha-helix conformation, the beta-sheet conformation, the beta-turn conformation, or some other (e.g. random coil) conformation.^{[11] [12]} These fractional assignments place important constraints on the possible secondary conformations that the protein can be in. CD cannot, in general, say where the alpha helices that are detected are located within the molecule or even completely predict how many there are. Despite this, CD is a valuable tool, especially for showing changes in conformation. It can, for instance, be used to study how the secondary structure of a molecule changes as a function of temperature or of the concentration of denaturing agents, e.g. Guanidinium hydrochloride or urea. In this way it can reveal important thermodynamic information about the molecule (such as the enthalpy and Gibbs free energy of denaturation) that cannot otherwise be easily obtained. Anyone attempting to study a protein will find CD a valuable tool for verifying that the protein is in its native conformation before undertaking extensive and/or expensive experiments with it. Also, there are a number of other uses for CD spectroscopy in protein chemistry not related to alpha-helix fraction estimation.

The near-UV CD spectrum (>250 nm) of proteins provides information on the tertiary structure. The signals obtained in the 250-300 nm region are due to the absorption, dipole orientation and the nature of the surrounding environment

of the phenylalanine, tyrosine, cysteine (or S-S disulfide bridges) and tryptophan amino acids. Unlike in far-UV CD, the near-UV CD spectrum cannot be assigned to any particular 3D structure. Rather, near-UV CD spectra provide structural information on the nature of the prosthetic groups in proteins, e.g., the heme groups in hemoglobin and cytochrome c.

Visible CD spectroscopy is a very powerful technique to study metal–protein interactions and can resolve individual d-d electronic transitions as separate bands. CD spectra in the visible light region are only produced when a metal ion is in a chiral environment, thus, free metal ions in solution are not detected. This has the advantage of only observing the protein-bound metal, so pH dependence and stoichiometries are readily obtained. Optical activity in transition metal ion complexes have been attributed to configurational, conformational and the vicinal effects. Klewpatinond and Viles (2007) have produced a set of empirical rules for predicting the appearance of visible CD spectra for Cu^{2+} and Ni^{2+} square-planar complexes involving histidine and main-chain coordination.

CD gives less specific structural information than X-ray crystallography and protein NMR spectroscopy, for example, which both give atomic resolution data. However, CD spectroscopy is a quick method that does not require large amounts of proteins or extensive data processing. Thus CD can be used to survey a large number of solvent conditions, varying temperature, pH, salinity, and the presence of various cofactors.

CD spectroscopy is usually used to study proteins in solution, and thus it complements methods that study the solid state. This is also a limitation, in that many proteins are embedded in membranes in their native state, and solutions containing membrane structures are often strongly scattering. CD is sometimes measured in thin films.

Experimental limitations

CD has also been studied in carbohydrates, but with limited success due to the experimental difficulties associated with measurement of CD spectra in the vacuum ultraviolet (VUV) region of the spectrum (100–200 nm), where the corresponding CD bands of unsubstituted carbohydrates lie. Substituted carbohydrates with bands above the VUV region have been successfully measured.

Measurement of CD is also complicated by the fact that typical aqueous buffer systems often absorb in the range where structural features exhibit differential absorption of circularly polarized light. Phosphate, sulfate, carbonate, and acetate buffers are generally incompatible with CD unless made extremely dilute e.g. in the 10–50 mM range. The TRIS buffer system should be completely avoided when performing far-UV CD. Borate and Onium compounds are often used to establish the appropriate pH range for CD experiments. Some experimenters have substituted fluoride for chloride ion because fluoride absorbs less in the far UV, and some have worked in pure water. Another, almost universal, technique is to minimize solvent absorption by using shorter path length cells when working in the far UV, 0.1 mm path lengths are not uncommon in this work.

In addition to measuring in aqueous systems, CD, particularly far-UV CD, can be measured in organic solvents e.g. ethanol, methanol, trifluoroethanol (TFE). The latter has the advantage to induce structure formation of proteins, inducing beta-sheets in some and alpha helices in others, which they would not show under normal aqueous conditions. Most common organic solvents such as acetonitrile, THF, chloroform, dichloromethane are however, incompatible with far-UV CD.

It may be of interest to note that the protein CD spectra used in secondary structure estimation are related to the π to π^* orbital absorptions of the amide bonds linking the amino acids. These absorption bands lie partly in the *so-called* vacuum ultraviolet (wavelengths less than about 200 nm). The wavelength region of interest is actually inaccessible in **air** because of the strong absorption of light by oxygen at these wavelengths. In practice these spectra are measured not in vacuum but in an oxygen-free instrument (filled with pure nitrogen gas).

Once oxygen has been eliminated, perhaps the second most important technical factor in working below 200 nm is to design the rest of the optical system to have low losses in this region. Critical in this regard is the use of aluminized mirrors whose coatings have been optimized for low loss in this region of the spectrum.

The usual light source in these instruments is a high pressure, short-arc xenon lamp. Ordinary xenon arc lamps are unsuitable for use in the low UV. Instead, specially constructed lamps with envelopes made from high-purity synthetic fused silica must be used.

Light from synchrotron sources has a much higher flux at short wavelengths, and has been used to record CD down to 160 nm. Recently the CD spectrometer at the electron storage ring facility ISA at the University of Aarhus in Denmark was used to record solid state CD spectra down to 120 nm.^[13] At the quantum mechanical level, the information content of circular dichroism and optical rotation are identical.

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Further reading

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External links

- Circular Dichroism explained (http://www.ap-lab.com/circular_dichroism.htm)
- Circular Dichroism at UMDNJ (<http://www2.umdj.edu/cdrwjweb/index.htm#software>) - a good site for information on structure estimation software
- Electromagnetic waves (<http://www.enzim.hu/~szia/cddemo/edemo1.htm>) - Animated electromagnetic waves. The Emanim program is a teaching resource for helping students understand the nature of electromagnetic waves and their interaction with birefringent and dichroic samples
- An Introduction to Circular Dichroism Spectroscopy (<http://www.photophysics.com/circulardichroism.php>) - a very good tutorial on circular dichroism spectroscopy

Optical rotatory dispersion

Optical rotatory dispersion is the variation in the optical rotation of a substance with a change in the wavelength of light. Optical rotatory dispersion can be used to find the absolute configuration of metal complexes. For example, when plane-polarized white light from an overhead projector is passed through a cylinder of sucrose solution, a spiral rainbow is observed perpendicular to the cylinder.

When white light passes through a polarizer, the extent of rotation of light depends on its wavelength. Short wavelengths are rotated more than longer wavelengths. Because the wavelength of light determines its color, the variation of color with distance through the tube is observed. This dependence of specific rotation on wavelength is called optical rotatory dispersion.

See also

- Circular dichroism

Spin polarization

Spin polarization is the degree to which the spin, i.e. the intrinsic angular momentum of elementary particles, is aligned with a given direction^[1]. This property may pertain to the spin, hence to the magnetic moment, of conduction electrons in ferromagnetic metals, such as iron, giving rise to spin polarized currents. It may refer to (static) spin waves, preferential correlation of spin orientation with ordered lattices (semiconductors or insulators).

It may also pertain to beams of particles, produced for particular aims, such as polarized neutron scattering or muon spin spectroscopy. Spin polarization of electrons or of nuclei, often called simply magnetization, is also produced by the application of a magnetic field, thanks to the Curie law and it is used to produce an induction signal in Electron spin resonance (ESR or EPR) and in Nuclear magnetic resonance (NMR).

Spin polarization is also important for spintronics, a branch of electronics. Magnetic semiconductors are being researched as possible spintronics materials.

The spin of free electrons is measured either by a LEED image from a clean wolfram-crystal (SPLEED)^{[2] [3] [4]} or by an electron microscope composed purely of electrostatic lenses and a gold foil as a sample. Back scattered electrons are decelerated by annular optics and focused onto a ring shaped electron mulitplier at about 15°. The position on the ring is recorded. This whole device is called a Mott-detector. Depending on their spin the electrons have the chance to hit the ring at different positions. 1% of the electrons are scattered in the foil. Of these 1% are collected by the detector and then about 30% of the electrons hit the detector at the wrong position. Both devices work due to spin orbit coupling.

The circular polarization of electromagnetic fields is due to spin polarization of their constituent photons.

In the most generic context, spin polarization is any alignment of the components of a non-scalar (vectorial, tensorial, spinor) field with its arguments, i.e., with the nonrelativistic three spatial or relativistic four spatiotemporal regions over which it is defined. In this sense, it also includes gravitational waves and any field theory that couples its constituents with the differential operators of vector analysis.

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Polarized Neutron Spectroscopy

Triple-axis spectrometry (TAS, T also resolved as "three", S also resolved as "spectroscopy") is a technique used in inelastic neutron scattering. The instrument is referred to as triple-axis spectrometer (also called TAS). It allows measurement of the scattering function at any point in energy and momentum space physically accessible by the spectrometer.

History

The triple-axis spectrometry method was first developed by Bertram Brockhouse at the NRX research reactor at the Chalk River Laboratories in Canada. The first results from the prototype triple-axis spectrometer were published in January 1955 and the first true triple-axis spectrometer was built in 1956. Bertram Brockhouse shared the 1994 Nobel prize for Physics for this development, which allowed elementary excitations, such as phonons and magnons, to be observed directly. The Nobel citation was "for pioneering contributions to the development of neutron scattering techniques for studies of condensed matter" and "for the development of neutron spectroscopy".

TAS Instruments in current use

FRM-II Forschungsneutronenquelle Heinz Maier-Leibnitz

- PANDA ^[1] - a cold neutron triple-axis spectrometer.
- PUMA ^[2] - a thermal neutron triple-axis spectrometer with multianalyser-detector option.

Helmholtz-Zentrum Berlin für Materialien und Energie

- FLEX ^[3] - a cold neutron triple-axis spectrometer with optional Neutron Resonance Spin Echo mode.
- E1 ^[4] - a thermal neutron triple-axis spectrometer with Polarization Analysis.

Institut Laue-Langevin

- IN1 ^[5] - a hot neutron triple-axis spectrometer.
 - IN3 ^[6] - a thermal neutron triple-axis spectrometer for tests.
 - IN8 ^[7] - a high-flux thermal neutron triple-axis spectrometer.
 - IN12 ^[8] - a cold neutron triple-axis spectrometer.
 - IN14 ^[9] - a cold neutron triple-axis spectrometer with polarized neutron capability.
 - IN20 ^[10] - a thermal neutron triple-axis spectrometer with polarized neutron capability.
 - IN22 ^[11] - a thermal neutron triple-axis spectrometer with polarized neutron capability.
 - D10 ^[12] - a thermal neutron four-circle diffractometer with a triple-axis energy analysis option.
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CEA/Saclay Laboratoire Léon Brillouin

- 1T-1^[13] - a double-focusing thermal neutron triple-axis spectrometer.
- 2T-1^[14] - a thermal neutron triple-axis spectrometer.
- 4F-1^[15] - a cold neutron triple-axis spectrometer.
- 4F-2^[16] - a cold neutron triple-axis spectrometer.

NIST Center for Neutron Research

- SPINS^[17] - a cold neutron triple-axis spectrometer with polarized neutron capability.
- BT-7^[18] - a thermal neutron triple-axis spectrometer with polarized neutron capability.
- BT-9^[18] - a thermal neutron triple-axis spectrometer.

MURR^[19] University of Missouri Research Reactor

- Triax^[20] - a thermal neutron triple-axis spectrometer.

External links

- Nobelprize.org page for the 1994 Nobel Prize for Physics^[21]

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- [3] https://www.helmholtz-berlin.de/user/neutrons/instrumentation/neutron-instruments/v2_en.html
- [4] https://www.helmholtz-berlin.de/user/neutrons/instrumentation/neutron-instruments/e1_en.html
- [5] <http://www.ill.fr/YellowBook/IN1/>
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Polarized Muon Spectroscopy

Muon spin spectroscopy is an experimental technique based on the implantation of spin polarized muons in matter and on the detection of the influence of the atomic, molecular or crystalline surroundings on their spin motion. The motion of the muon spin is due to the magnetic field experienced by the particle and may provide information on its local environment in a very similar way to other magnetic resonance techniques, such as electron spin resonance (ESR or EPR) and, more closely, nuclear magnetic resonance (NMR).

Acronym

In analogy with the acronyms for these previously established spectroscopies, the muon spin spectroscopy is also known as μ SR, which stands for **muon spin rotation**, or relaxation, or resonance, depending respectively on whether the muon spin motion is predominantly a rotation (more precisely a precession around a still magnetic field), or a relaxation towards an equilibrium direction, or, again, a more complex dynamics dictated by the addition of short radio frequency pulses.

How it works

The time scale on which the spin motion may be exploited is that of the muon decay, *i.e.* a few mean lifetimes, each roughly 2.2 μ s (2.2 millionths of a second). Both the production of muon beams with nearly perfect alignment of the spin to the beam direction (what was referred to above as spin polarization and caused by the spontaneous symmetry breaking), and the ability to detect the muon spin direction at the instant of the muon decay rely on the violation of parity, which takes place whenever weak forces are at play.

In short this means that certain elementary events happen only when including clockwise (or only when including counterclockwise) rotations. For instance, the positive muon decays into a positron plus two neutrinos and the positron is preferentially emitted in the direction of the muon spin. Therefore it would most often *see* the spin as a counterclockwise rotation while flying away from the decay point.

Spin alignment allows the production of a muon beam with an aligned magnetic moment. Muons are injected into the material under investigation as short-lived *spies* sending information from the interior back out to the experimental apparatus. These muons are able to send a message from inside the crystal about the local magnetic field in their surroundings. After some time (mean lifetime 2.2 μ s) these spies decay and emit positrons. A beam of aligned muons produces asymmetric positron radiation. The asymmetry of positron radiation contains information about the direction of local magnetic field in the moment of muon decay. Taking into consideration the initial direction of muon magnetic moment and the time interval between the moment of injection and moment of muon decay we can calculate the precession frequency (how rapidly the muon's magnetic moment rotates). The frequency of magnetic moment precession depends on the local magnetic field. Larmor precession is appeared with z -direction magnetic field and only decay in 2.2 μ s. But when x -direction magnetic field is applied in muon, the rate of decay is enhanced by gaussian with depolarization rate.

Since 1987 this method was used to measure internal magnetic fields inside high-temperature superconductors. High-temperature superconductors are Type II superconductors, in which the local magnetic fields inside the superconductor depend on the superconducting carrier density—one of the significant parameters of any superconductor (see for example the Bardeen–Cooper–Shrieffer theory of superconductors).

Applications

Muon Spin Rotation and Relaxation are mostly performed with positive muons. They are well suited to the study of magnetic fields at the atomic scale inside matter, such as those produced by various kinds of magnetism and/or superconductivity encountered in compounds occurring in nature or artificially produced by modern material science.

The London penetration depth is one of the most important parameters characterizing a superconductor because its inverse square provides a measure of the density n_s of Cooper pairs. The dependence of n_s on temperature and magnetic field directly indicates the symmetry of the superconducting gap. Muon spin spectroscopy provides a way to measure the penetration depth, and so has been used to study high-temperature cuprate superconductors since their discovery in 1986.

Other important fields of application of μ SR exploit the fact that positive muons capture electrons to form muonium atoms which behave chemically as light isotopes of the hydrogen atom. This allows investigation of the largest known "isotope effect" in some of the simplest types of chemical reactions, as well as the early stages of formation of radicals in organic chemicals. Muonium is also studied as an analogue of hydrogen in semiconductors, where hydrogen is one of the most ubiquitous impurities.

Facilities

μ SR requires a particle accelerator for the production of a muon beam. This is presently achieved at few large scale facilities in the world: the CMMS continuous source at TRIUMF in Vancouver, Canada; the LMU continuous source at the Paul Scherrer Institut (PSI) in Villigen, Switzerland; the ISIS and RIKEN-RAL pulsed sources at the Rutherford Appleton Laboratory in Chilton, United Kingdom; and the J-PARC facility in Tokai, Japan, where a new pulsed source is being built to replace that at KEK in Tsukuba, Japan. Muon beams are also available at the Laboratory of Nuclear Problems, Joint Institute for Nuclear Research (JINR) in Dubna, Russia. The International Society for μ SR Spectroscopy (ISMS) exists to promote the worldwide advancement of μ SR. Membership in the society is open free of charge to all individuals in academia, government laboratories and industry who have an interest in the society's goals.

External links

- ISIS Introductory course in μ SR ^[1]
- introduction to μ SR ^[2]
- μ SR Brochure ^[3] (a 3.2 MB PDF file)
- CMMS ^[4]: TRIUMF Center for Molecular and Materials Science

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- [3] <http://muon.neutron-eu.net/muon/files/muSRBrochure.pdf>
- [4] <http://musr.org/>
-

Time-resolved spectroscopy

In physics and physical chemistry, **time-resolved spectroscopy** is the study of dynamic processes in materials or chemical compounds by means of spectroscopic techniques. Most often, processes are studied that occur after illumination of a material, but in principle, the technique can be applied to any process that leads to a change in properties of a material. With the help of pulsed lasers, it is possible to study processes that occur on time scales as short as 10^{-14} seconds. The rest of the article discusses different types of time-resolved spectroscopy.

Transient-absorption spectroscopy

Transient-absorption spectroscopy is an extension of absorption spectroscopy. Here, the absorbance at a particular wavelength or range of wavelengths of a sample is measured as a function of time after excitation by a flash of light. In a typical experiment, both the light for excitation ('pump') and the light for measuring the absorbance ('probe') are generated by a pulsed laser. If the process under study is slow, then the time resolution can be obtained with a continuous (i.e., not pulsed) probe beam and repeated conventional spectrophotometric techniques.

Examples of processes that can be studied:

- Optical gain spectroscopy of semiconductor laser materials.
- Chemical reactions that are initiated by light (or 'photoinduced chemical reactions');
- The transfer of excitation energy between molecules, parts of molecules, or molecules and their environment;
- The behaviour of electrons that are freed from a molecule or crystalline material.

Other multiple-pulse techniques

Transient spectroscopy as discussed above is a technique that involves two pulses. There are many more techniques that employ two or more pulses, such as:

- Photon echoes.
- Four-wave mixing (involves three laser pulses)

The interpretation of experimental data from these techniques is usually much more complicated than in transient-absorption spectroscopy.

Nuclear magnetic resonance and electron spin resonance are often implemented with multiple-pulse techniques, though with radio waves and micro waves instead of visible light.

Time-resolved infrared spectroscopy

Time-resolved infrared (TRIR) spectroscopy also employs a two-pulse, "pump-probe" methodology. The pump pulse is typically in the UV region and is often generated by a high-powered Nd:YAG laser, whereas the probe beam is in the infrared region. This technique currently operates down to the picosecond time regime and surpasses transient absorption and emission spectroscopy by providing *structural* information on the excited-state kinetics of both dark and emissive states.

Time-resolved fluorescence spectroscopy

Time-resolved fluorescence spectroscopy is an extension of fluorescence spectroscopy. Here, the fluorescence of a sample is monitored as a function of time after excitation by a flash of light. The time resolution can be obtained in a number of ways, depending on the required sensitivity and time resolution:

- With fast-detection electronics (nanoseconds and slower)
- With a streak camera (picoseconds and slower)
- With optical gating (femtoseconds-nanoseconds) - a short laser pulse acts as a gate for the detection of fluorescence light; only fluorescence light that arrives at the detector at the same time as the gate pulse is detected. This technique has the best time resolution, but the efficiency is rather low. An extension of this optical gating technique is to use a "Kerr gate", which allows the scattered Raman signal to be collected before the (slower) fluorescence signal overwhelms it. This technique can greatly improve the signal:noise ratio of Raman spectra.

Terahertz spectroscopy

Terahertz frequency radiation for spectroscopy is typically generated in one of three ways:

- time domain terahertz spectroscopy (TDTS), using ultrashort laser pulses
- photomixing, mixing two radiation sources to generate their difference frequency
- Fourier transform spectroscopy, using a blackbody radiation source

Atomic absorption spectroscopy

Atomic absorption spectrometry (AAS) is a spectroanalytical procedure for the qualitative and quantitative determination of chemical elements employing the absorption of optical radiation (light) by free atoms in the gaseous state. In analytical chemistry the technique is used for determining the concentration of a particular element (the analyte) in a sample to be analyzed. AAS can be used to determine over 70 different elements in



novAA series - Atomic absorption spectrometers by **Analytik Jena**

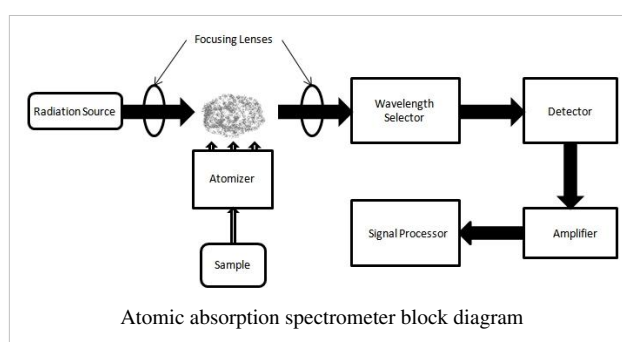
solution or directly in solid samples. Atomic absorption spectrometry was first used as an analytical technique, and the underlying principles were established in the second half of the 19th century by Robert Wilhelm Bunsen and Gustav Robert Kirchhoff, both professors at the University of Heidelberg, Germany. The modern form of AAS was largely developed during the 1950s by a team of Australian Chemists. They were led by Sir Alan Walsh at the CSIRO (Commonwealth Scientific and Industrial Research Organization), Division of Chemical Physics, in Melbourne, Australia.

Principles

The technique makes use of absorption spectrometry to assess the concentration of an analyte in a sample. It requires standards with known analyte content to establish the relation between the measured absorbance and the analyte concentration and relies therefore on Beer-Lambert Law. In short, the electrons of the atoms in the atomizer can be promoted to higher orbitals (excited state) for a short period of time (nanoseconds) by absorbing a defined quantity of energy (radiation of a given wavelength). This amount of energy, i.e., wavelength, is specific to a particular electron transition in a particular element. In general, each wavelength corresponds to only one element, and the width of an absorption line is only of the order of a few picometers (pm), which gives the technique its elemental selectivity. The radiation flux without a sample and with a sample in the atomizer is measured using a detector, and the ratio between the two values (the absorbance) is converted to analyte concentration or mass using Beer-Lambert Law.

Instrumentation

In order to analyze a sample for its atomic constituents, it has to be atomized. The sample should then be illuminated by light. The light transmitted in order to determine the content of a given analyte in a sample, it has to be atomized. The atomizers most commonly used nowadays are flames and electrothermal (graphite tube) atomizers. The atoms should then be irradiated by optical radiation, and the radiation source could be an element-specific line radiation source or a continuum radiation source. The radiation then passes through a monochromator in order to separate the element-specific radiation from any other radiation emitted by the radiation source, which is finally measured by a detector.



Atomizers

Although other atomizers, such as heated quartz tubes, might be used for special purposes, the atomizers most commonly used nowadays are (spectroscopic) flames and electrothermal (graphite tube) atomizers.

Flame atomizers

The oldest and most commonly used atomizers in AAS are flames, principally the air-acetylene flame with a temperature of about 2300 °C and the nitrous oxide (N₂O)-acetylene flame with a temperature of about 2700 °C. The latter flame, in addition, offers a more reducing environment, being ideally suited for analytes with high affinity to oxygen.

Liquid or dissolved samples are typically used with flame atomizers. The sample solution is aspirated by a pneumatic nebulizer, transformed into an aerosol, which is introduced into a spray chamber, where it is mixed with the flame gases and conditioned in a way that only the finest aerosol droplets (< 10 µm) enter the flame. This conditioning process is responsible that only about 5% of the aspirated sample solution reaches the flame, but it also guarantees a relatively high freedom from interference.

On top of the spray chamber is a burner head that produces a flame that is laterally long (usually 5–10 cm) and only a few mm deep. The radiation beam passes through this flame at its longest axis, and the flame gas flow-rates may be adjusted to produce the highest concentration of free atoms. The burner height may also be adjusted, so that the radiation beam passes through the zone of highest atom cloud density in the flame, resulting in the highest sensitivity.

The processes in a flame include the following stages:

- Desolvation (drying) – the solvent is evaporated and the dry sample nano-particles remain;
- Vaporization (transfer to the gaseous phase) – the solid particles are converted into gaseous molecules;
- Atomization – the molecules are dissociated into free atoms;
- Ionization – depending on the ionization potential of the analyte atoms and the energy available in a particular flame, atoms might be in part converted to gaseous ions.

Each of these stages includes the risk of interference in case the degree of phase transfer is different for the analyte in the calibration standard and in the sample. Ionization is generally undesirable, as it reduces the number of atoms that is available for measurement, i.e., the sensitivity. In flame AAS a steady-state signal is generated during the time period when the sample is aspirated. This technique is typically used for determinations in the mg L⁻¹ range, and may be extended down to a few µg L⁻¹ for some elements.

Electrothermal atomizers

Electrothermal AAS (ET AAS) using graphite tube atomizers was pioneered by Boris V. L'vov at the Leningrad Polytechnical Institute, Russia, since the late 1950s, and further investigated by Hans Massmann at the Institute of Spectrochemistry and Applied Spectroscopy (ISAS) in Dortmund, Germany.

Although a wide variety of graphite tube designs have been used over the years, the dimensions nowadays are typically 20–25 mm in length and 5–6 mm inner diameter. With this technique liquid/dissolved, solid and gaseous samples may be analyzed directly. A measured volume (typically 10–50 µL) or a weighed mass (typically around 1 mg) of a solid sample are introduced into the graphite tube and subject to a temperature program. This typically consists of stages, such as:

- Drying – the solvent is evaporated
- Pyrolysis – the majority of the matrix constituents is removed
- Atomization – the analyte element is released to the gaseous phase
- Cleaning – eventual residues in the graphite tube are removed at high temperature.

The graphite tubes are heated via their ohmic resistance using a low-voltage high-current power supply; the temperature in the individual stages can be controlled very closely, and temperature ramps between the individual stages facilitate separation of sample components. Tubes may be heated transversely or longitudinally, where the former ones have the advantage of a more homogeneous temperature distribution over their length. The so-called Stabilized Temperature Platform Furnace (STPF) concept, proposed by Walter Slavin, based on research of Boris L'vov, makes ET AAS essentially free from interference. The major components of this concept are:

- Atomization of the sample from a graphite platform inserted into the graphite tube (L'vov platform) instead of from the tube wall in order to delay atomization until the gas phase in the atomizer has reached a stable temperature;
- Use of a chemical modifier in order to stabilize the analyte to a pyrolysis temperature that is sufficient to remove the majority of the matrix components;
- Integration of the absorbance over the time of the transient absorption signal instead of using peak height absorbance for quantification.

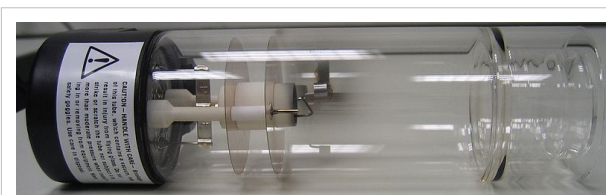
In ET AAS a transient signal is generated, the area of which is directly proportional to the mass of analyte (not its concentration) introduced into the graphite tube. This technique has the advantage that any kind of sample, solid, liquid or gaseous, can be analyzed directly. Its sensitivity is 2–3 orders of magnitude higher than that of flame AAS, so that determinations in the low µg L⁻¹ range (for a typical sample volume of 20 µL) and ng g⁻¹ range (for a typical sample mass of 1 mg) can be carried out. It shows a very high degree of freedom from interferences, so that ET AAS might be considered the most robust technique available nowadays for the determination of trace elements in complex matrices.

Radiation sources

We have to distinguish between line source AAS (LS AAS) and continuum source AAS (CS AAS). In classical LS AAS, as it has been proposed by Alan Walsh, the high spectral resolution required for AAS measurements is provided by the radiation source itself that emits the spectrum of the analyte in the form of lines that are narrower than the absorption lines. Continuum sources, such as deuterium lamps, are only used for background correction purposes. The advantage of this technique is that only a medium-resolution monochromator is necessary for measuring AAS; however, it has the disadvantage that usually a separate lamp is required for each element that has to be determined. In CS AAS, in contrast, a single lamp, emitting a continuum spectrum over the entire spectral range of interest is used for all elements. Obviously, a high-resolution monochromator is required for this technique, as will be discussed later.

Hollow cathode lamps

Hollow cathode lamps (HCL) are the most common radiation source in LS AAS. Inside the sealed lamp, filled with argon or neon gas at low pressure, is a cylindrical metal cathode containing the element of interest and an anode. A high voltage is applied across the anode and cathode, resulting in an ionization of the fill gas. The gas ions are accelerated towards the cathode and, upon impact on the cathode, sputter cathode material that is excited in the glow discharge to emit the radiation of the sputtered material, i.e., the element of interest.



Hollow cathode lamp (HCL)

Electrodeless discharge lamps

Electrodeless discharge lamps (EDL) contain a small quantity of the analyte as a metal or a salt in a quartz bulb together with an inert gas, typically argon, at low pressure. The bulb is inserted into a coil that is generating an electromagnetic radio frequency field, resulting in a low-pressure inductively coupled discharge in the lamp. The emission from an EDL is higher than that from an HCL, and the line width is generally narrower, but EDLs need a separate power supply and might need a longer time to stabilize.

Deuterium lamps

Deuterium HCL or even hydrogen HCL and deuterium discharge lamps are used in LS AAS for background correction purposes. The radiation intensity emitted by these lamps is decreasing significantly with increasing wavelength, so that they can be only used in the wavelength range between 190 and about 320 nm.

Continuum sources

When a continuum radiation source is used for AAS, it is necessary to use a high-resolution monochromator, as will be discussed later. In addition it is necessary that the lamp emits radiation of intensity at least an order of magnitude above that of a typical HCL over the entire wavelength range from 190 nm to 900 nm. A special high-pressure xenon short arc lamp, operating in a hot-spot mode has been developed to fulfill these requirements.

Spectrometer

As already pointed out above, we have to distinguish between medium-resolution spectrometers that are used for LS AAS and high-resolution spectrometers that are designed for CS AAS. The spectrometer includes the spectral sorting device (monochromator) and the detector.

Spectrometers for LS AAS

In LS AAS the high resolution that is required for the measurement of atomic absorption is provided by the narrow line emission of the radiation source, and the monochromator simply has to resolve the analytical line from other radiation emitted by the lamp. This can usually be accomplished with a band pass between 0.2 and 2 nm, i.e., a medium-resolution monochromator. Another feature to make LS AAS element-specific is modulation of the primary radiation and the use of a selective amplifier that is tuned to the same modulation frequency, as already postulated by Alan Walsh. This way any (unmodulated) radiation emitted for example by the atomizer can be excluded, which is imperative for LS AAS. Simple monochromators of the Littrow or (better) the Czerny-Turner design are typically used for LS AAS. Photomultiplier tubes are the most frequently used detectors in LS AAS, although solid state detectors might be preferred because of their better signal-to-noise ratio.

Spectrometers for CS AAS

When a continuum radiation source is used for AAS measurement it is indispensable to work with a high-resolution monochromator. The resolution has to be equal to or better than the half width of an atomic absorption line (about 2 pm) in order to avoid losses of sensitivity and linearity of the calibration graph. The research with high-resolution (HR) CS AAS was pioneered by the groups of O'Haver and Harnly in the USA, who also developed the (up until now) only simultaneous multi-element spectrometer for this technique. The break-through, however, came when the group of Becker-Ross in Berlin, Germany, built a spectrometer entirely designed for HR-CS AAS. The first commercial equipment for HR-CS AAS was introduced by **Analytik Jena** (Jena, Germany) at the beginning of the 21st century, based on the design proposed by Becker-Ross and Florek. These spectrometers use a compact double monochromator with a prism pre-monochromator and an echelle grating monochromator for high resolution. A



Xenon lamp as a continuous radiation source

linear charge coupled device (CCD) array with 200 pixels is used as the detector. The second monochromator does not have an exit slit; hence the spectral environment at both sides of the analytical line becomes visible at high resolution. As typically only 3–5 pixels are used to measure the atomic absorption, the other pixels are available for correction purposes. One of these corrections is that for lamp flicker noise, which is independent of wavelength, resulting in measurements with very low noise level; other corrections are those for background absorption, as will be discussed later.

Background absorption and background correction

The relatively small number of atomic absorption lines (compared to atomic emission lines) and their narrow width (a few pm) make spectral overlap rare; there are only very few examples known that an absorption line from one element will overlap with another. Molecular absorption, in contrast, is much broader, so that it is more likely that some molecular absorption band will overlap with an atomic line. This kind of absorption might be caused by un-dissociated molecules of concomitant elements of the sample or by flame gases. We have to distinguish between the spectra of di-atomic molecules, which exhibit a pronounced fine structure, and those of larger (usually tri-atomic) molecules that don't show such fine structure. Another source of background absorption, particularly in ET AAS, is scattering of the primary radiation at particles that are generated in the atomization stage, when the matrix could not be removed sufficiently in the pyrolysis stage.

All these phenomena, molecular absorption and radiation scattering, can result in artificially high absorption and an improperly high (erroneous) calculation for the concentration or mass of the analyte in the sample. There are several techniques available to correct for background absorption, and they are significantly different for LS AAS and HR-CS AAS.

Background correction techniques in LS AAS

In LS AAS background absorption can only be corrected using instrumental techniques, and all of them are based on two sequential measurements, firstly, total absorption (atomic plus background), secondly, background absorption only, and the difference of the two measurements gives the net atomic absorption. Because of this, and because of the use of additional devices in the spectrometer, the signal-to-noise ratio of background-corrected signals is always significantly inferior compared to uncorrected signals. It should also be pointed out that in LS AAS there is no way to correct for (the rare case of) a direct overlap of two atomic lines. In essence there are three techniques used for background correction in LS AAS:

Deuterium background correction

This is the oldest and still most commonly used technique, particularly for flame AAS. In this case, a separate source (a deuterium lamp) with broad emission is used to measure the background absorption over the entire width of the exit slit of the spectrometer. The use of a separate lamp makes this technique the least accurate one, as it cannot correct for any structured background. It also cannot be used at wavelengths above about 320 nm, as the emission intensity of the deuterium lamp becomes very weak. The use of deuterium HCL is preferable compared to an arc lamp due to the better fit of the image of the former lamp with that of the analyte HCL.

Smith-Hieftje background correction

This technique (named after their inventors) is based on the line-broadening and self-reversal of emission lines from HCL when high current is applied. Total absorption is measured with normal lamp current, i.e., with a narrow emission line, and background absorption after application of a high-current pulse with the profile of the self-reversed line, which has little emission at the original wavelength, but strong emission on both sides of the analytical line. The advantage of this technique is that only one radiation source is used; among the disadvantages are that the high-current pulses reduce lamp lifetime, and that the technique can only be used for relatively volatile

elements, as only those exhibit sufficient self-reversal to avoid dramatic loss of sensitivity. Another problem is that background is not measured at the same wavelength as total absorption, making the technique unsuitable for correcting structured background.

Zeeman-effect background correction

An alternating magnetic field is applied at the atomizer (graphite furnace) to split the absorption line into three components, the π component, which remains at the same position as the original absorption line, and two σ components, which are moved to higher and lower wavelengths, respectively (see Zeeman Effect). Total absorption is measured without magnetic field and background absorption with the magnetic field on. The π component has to be removed in this case, e.g. using a polarizer, and the σ components do not overlap with the emission profile of the lamp, so that only the background absorption is measured. The advantage of this technique is that total and background absorption are measured with the same emission profile of the same lamp, so that any kind of background, including background with fine structure can be corrected accurately, unless the molecule responsible for the background is also affected by the magnetic field; the disadvantage is the increased complexity of the spectrometer.

Background correction techniques in HR-CS AAS

In HR-CS AAS background correction is carried out mathematically in the software using information from detector pixels that are not used for measuring atomic absorption; hence, in contrast to LS AAS, no additional components are required for background correction.

Background correction using correction pixels

It has already been mentioned that in HR-CS AAS lamp flicker noise is eliminated using correction pixels. In fact, any increase or decrease in radiation intensity that is observed to the same extent at all pixels chosen for correction is eliminated by the correction algorithm. This obviously also includes a reduction of the measured intensity due to radiation scattering or molecular absorption, which is corrected in the same way. As measurement of total and background absorption, and correction for the latter, are strictly simultaneous (in contrast to LS AAS), even the fastest changes of background absorption, as they may be observed in ET AAS, do not cause any problem. In addition, as the same algorithm is used for background correction and elimination of lamp noise, the background corrected signals show a much better signal-to-noise ratio compared to the uncorrected signals, which is also in contrast to LS AAS.

Background correction using a least-squares algorithm

The above technique can obviously not correct for a background with fine structure, as in this case the absorbance will be different at each of the correction pixels. In this case HR-CS AAS is offering the possibility to measure correction spectra of the molecule(s) that is (are) responsible for the background and store them in the computer. These spectra are then multiplied with a factor to match the intensity of the sample spectrum and subtracted pixel by pixel and spectrum by spectrum from the sample spectrum using a least-squares algorithm. This might sound



Analytik Jena's HR-CS AAS

complex, but first of all the number of di-atomic molecules that can exist at the temperatures of the atomizers used in AAS is relatively small, and second, the correction is performed by the computer within a few seconds. The same algorithm can actually also be used to correct for direct line overlap of two atomic absorption lines, making HR-CS AAS the only AAS technique that can correct for this kind of spectral interference.

See also

- Beer-Lambert law
- Laser absorption spectrometry
- JAAS Journal of Analytical Atomic Spectrometry
- Vapour phase decomposition
- Inductively coupled plasma mass spectrometry

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Fourier transform spectroscopy

Fourier transform spectroscopy is a measurement technique whereby spectra are collected based on measurements of the coherence of a radiative source, using time-domain or space-domain measurements of the electromagnetic radiation or other type of radiation. It can be applied to a variety of types of spectroscopy including optical spectroscopy, infrared spectroscopy (FTIR, FT-NIRS), nuclear magnetic resonance (NMR) and magnetic resonance spectroscopic imaging (MRSI)^[1], mass spectrometry and electron spin resonance spectroscopy. There are several methods for measuring the temporal coherence of the light (see: field-autocorrelation), including the continuous wave *Michelson* or *Fourier transform* spectrometer and the pulsed Fourier transform spectrograph (which is more sensitive and has a much shorter sampling time than conventional spectroscopic techniques, but is only applicable in a laboratory environment).

The term *Fourier transform spectroscopy* reflects the fact that in all these techniques, a Fourier transform is required to turn the raw data into the actual spectrum, and in many of the cases in optics involving interferometers, is based on the Wiener–Khinchin theorem.

Conceptual introduction

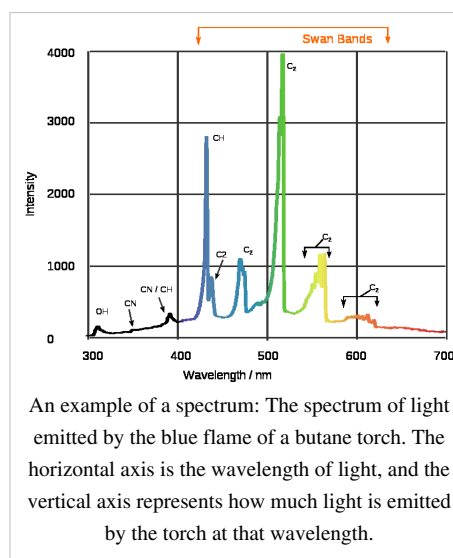
Measuring an emission spectrum

One of the most basic tasks in spectroscopy is to characterize the spectrum of a light source: How much light is emitted at each different wavelength. The most straightforward way to measure a spectrum is to pass the light through a monochromator, an instrument that blocks all of the light *except* the light at a certain wavelength (the un-blocked wavelength is set by a knob on the monochromator). Then the intensity of this remaining (single-wavelength) light is measured. The measured intensity directly indicates how much light is emitted at that wavelength. By varying the monochromator's wavelength setting, the full spectrum can be measured. This simple scheme in fact describes how *some* spectrometers work.

Fourier transform spectroscopy is a less intuitive way to get the same information. Rather than allowing only one wavelength at a time to pass through to the detector, this technique lets through a beam containing many different wavelengths of light at once, and measures the *total* beam intensity. Next, the beam is modified to contain a *different* combination of wavelengths, giving a second data point. This process is repeated many times. Afterwards, a computer takes all this data and works backwards to infer how much light there is at each wavelength.

To be more specific, between the light source and the detector, there is a certain configuration of mirrors that allows some wavelengths to pass through but blocks others (due to wave interference). The beam is modified for each new data point by moving one of the mirrors; this changes the set of wavelengths that can pass through.

As mentioned, computer processing is required to turn the raw data (light intensity for each mirror position) into the desired result (light intensity for each wavelength). The processing required turns out to be a common algorithm called the Fourier transform (hence the name, "Fourier transform spectroscopy"). The raw data is sometimes called an "interferogram".



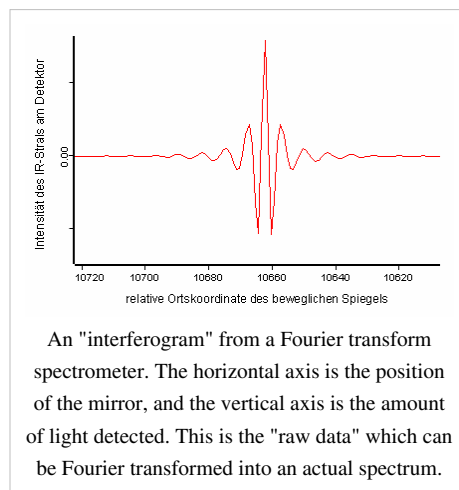
An example of a spectrum: The spectrum of light emitted by the blue flame of a butane torch. The horizontal axis is the wavelength of light, and the vertical axis represents how much light is emitted by the torch at that wavelength.

Measuring an absorption spectrum

The method of Fourier transform spectroscopy can also be used for absorption spectroscopy. The primary example is "FTIR Spectroscopy", a common technique in chemistry.

In general, the goal of absorption spectroscopy is to measure how well a sample absorbs or transmits light at each different wavelength. Although absorption spectroscopy and emission spectroscopy are different in principle, they are closely related in practice; any technique for emission spectroscopy can also be used for absorption spectroscopy. First, the emission spectrum of a broadband lamp is measured (this is called the "background spectrum"). Second, the emission spectrum of the same lamp *shining through the sample* is measured (this is called the "sample spectrum"). The sample will absorb some of the light, causing the spectra to be different. The ratio of the "sample spectrum" to the "background spectrum" is directly related to the sample's absorption spectrum.

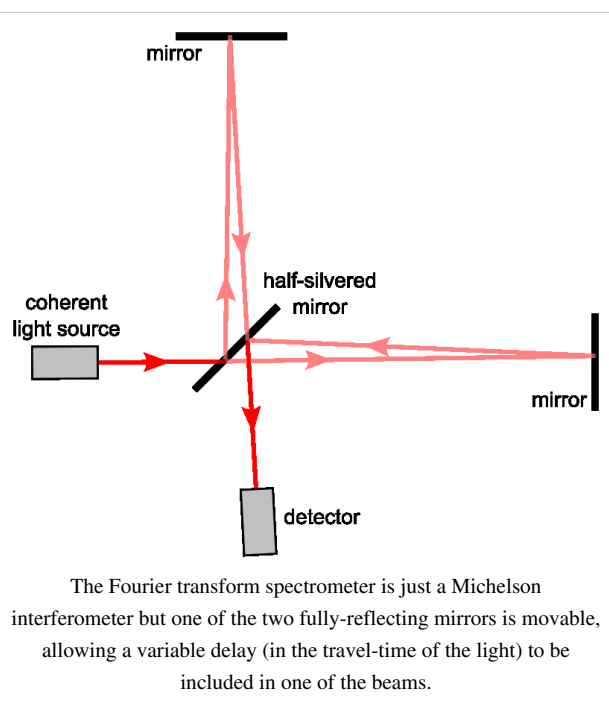
Accordingly, the technique of "Fourier transform spectroscopy" can be used both for measuring emission spectra (for example, the emission spectrum of a star), *and* absorption spectra (for example, the absorption spectrum of a glass of liquid).



Continuous wave *Michelson* or *Fourier transform* spectrograph

The Michelson spectrograph is similar to the instrument used in the Michelson-Morley experiment. Light from the source is split into two beams by a half-silvered mirror, one is reflected off a fixed mirror and one off a moving mirror which introduces a time delay—the Fourier transform spectrometer is just a Michelson interferometer with a movable mirror. The beams interfere, allowing the temporal coherence of the light to be measured at each different time delay setting, effectively converting the time domain into a spatial coordinate. By making measurements of the signal at many discrete positions of the moving mirror, the spectrum can be reconstructed using a Fourier transform of the temporal coherence of the light. Michelson spectrographs are capable of very high spectral resolution observations of very bright sources. The Michelson or Fourier transform spectrograph was popular for infra-red applications at a time when infra-red astronomy only had single pixel detectors.

Imaging Michelson spectrometers are a possibility, but in general have been supplanted by imaging Fabry–Pérot instruments which are easier to construct.



Extracting the spectrum

The intensity as a function of the path length difference in the interferometer p and wavenumber $\tilde{\nu} = 1/\lambda$ is^[2]

$$I(p, \tilde{\nu}) = I(\tilde{\nu})[1 + \cos(2\pi\tilde{\nu}p)],$$

where $I(\tilde{\nu})$ is the spectrum to be determined. Note that it is not necessary for $I(\tilde{\nu})$ to be modulated by the sample before the interferometer. In fact, most FTIR spectrometers place the sample after the interferometer in the optical path. The total intensity at the detector is

$$I(p) = \int_0^\infty I(p, \tilde{\nu}) d\tilde{\nu} = \int_0^\infty I(\tilde{\nu})[1 + \cos(2\pi\tilde{\nu}p)] d\tilde{\nu}.$$

This is just a Fourier cosine transform. The inverse gives us our desired result in terms of the measured quantity $I(p)$:

$$I(\tilde{\nu}) = 4 \int_0^\infty [I(p) - \frac{1}{2}I(p=0)] \cos(2\pi\tilde{\nu}p) dp.$$

Pulsed Fourier transform spectrometer

A pulsed *Fourier transform* spectrometer does not employ transmittance techniques. In the most general description of pulsed FT spectrometry, a sample is exposed to an energizing event which causes a periodic response. The frequency of the periodic response, as governed by the field conditions in the spectrometer, is indicative of the measured properties of the analyte.

Examples of pulsed Fourier transform spectrometry

In magnetic spectroscopy (EPR, NMR), an RF pulse in a strong ambient magnetic field is used as the energizing event. This turns the magnetic particles at an angle to the ambient field, resulting in gyration. The gyrating spins then induce a periodic current in a detector coil. Each spin exhibits a characteristic frequency of gyration (relative to the field strength) which reveals information about the analyte.

In Fourier transform mass spectrometry, the energizing event is the injection of the charged sample into the strong electromagnetic field of a cyclotron. These particles travel in circles, inducing a current in a fixed coil on one point in their circle. Each traveling particle exhibits a characteristic cyclotron frequency-field ratio revealing the masses in the sample.

Free induction decay

Pulsed FT spectrometry gives the advantage of requiring a single, time-dependent measurement which can easily deconvolute a set of similar but distinct signals. The resulting composite signal, is called a *free induction decay*, because typically the signal will decay due to inhomogeneities in sample frequency, or simply unrecoverable loss of signal due to entropic loss of the property being measured.

Stationary forms of Fourier transform spectrometers

In addition to the scanning forms of Fourier transform spectrometers, there are a number of stationary or self-scanned forms.^[3] While the analysis of the interferometric output is similar to that of the typical scanning interferometer, significant differences apply, as shown in the published analyses. Some stationary forms retain the Fellgett multiplex advantage, and their use in the spectral region where detector noise limits apply is similar to the scanning forms of the FTS. In the photon-noise limited region, the application of stationary interferometers is dictated by specific consideration for the spectral region and the application.

Fellgett advantage

One of the most important advantages of Fourier transform spectroscopy was shown by P.B. Fellgett, an early advocate of the method. The Fellgett advantage, also known as the multiplex principle, states that when obtaining a spectrum when measurement noise is dominated by detector noise, a multiplex spectrometer such as a Fourier transform spectrometer will produce a relative improvement in signal-to-noise ratio, compared to an equivalent scanning monochromator, of the order of the square root of m , where m is the number of sample points comprising the spectrum.

Converting spectra from time domain to frequency domain

$$S(t) = \int_{-\infty}^{\infty} I(\nu) e^{-i\nu 2\pi t} d\nu$$

The sum is performed over all contributing frequencies to give a signal $S(t)$ in the time domain.

$$I(\nu) = \int_{-\infty}^{\infty} S(t) e^{i\nu 2\pi t} dt$$

gives non-zero value when $S(t)$ contains a component that matches the oscillating function.

Remember that

$$e^{ix} = \cos x + i \sin x$$

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- [2] Peter Atkins, Julio De Paula. 2006. *Physical Chemistry*, 8th ed. Oxford University Press: Oxford, UK.
- [3] William H. Smith U.S. Patent 4976542 (<http://www.google.com/patents?vid=4976542>) Digital Array Scanned Interferometer, issued Dec. 11, 1990

External links

- Description of how a Fourier transform spectrometer works (<http://scienceworld.wolfram.com/physics/FourierTransformSpectrometer.html>)
- The Michelson or Fourier transform spectrograph (<http://www.astro.livjm.ac.uk/courses/phys362/notes/>)
- Internet Journal of Vibrational Spectroscopy - How FTIR works (<http://www.ijvs.com/volume5/edition5/section1.html#Feature>)
- Fourier Transform Spectroscopy Topical Meeting and Tabletop Exhibit (<http://www.osa.org/meetings/topicalmeetings/fts/default.aspx>)

Nuclear magnetic resonance

Nuclear magnetic resonance (NMR) is a property that magnetic nuclei have in a magnetic field and applied electromagnetic (EM) pulse or pulses, which cause the nuclei to absorb energy from the EM pulse and radiate this energy back out. The energy radiated back out is at a specific resonance frequency which depends on the strength of the magnetic field and other factors. This allows the observation of specific quantum mechanical magnetic properties of an atomic nucleus. Many scientific techniques exploit NMR phenomena to study molecular physics, crystals and non-crystalline materials through NMR spectroscopy. NMR is also routinely used in advanced medical imaging techniques, such as in magnetic resonance imaging (MRI).

All stable isotopes that contain an odd number of protons and/or of neutrons (see Isotope) have an intrinsic magnetic moment and angular momentum, in other words a nonzero spin, while all nuclides with even numbers of both have spin 0. The most commonly studied nuclei are ^1H (the most NMR-sensitive isotope after the radioactive ^3H) and ^{13}C , although nuclei from isotopes of many other elements (e.g. ^2H , ^{10}B , ^{11}B , ^{14}N , ^{15}N , ^{17}O , ^{19}F , ^{23}Na , ^{29}Si , ^{31}P , ^{35}Cl , ^{113}Cd , ^{129}Xe , ^{195}Pt) are studied by high-field NMR spectroscopy as well.

A key feature of NMR is that the resonance frequency of a particular substance is directly proportional to the strength of the applied magnetic field. It is this feature that is exploited in imaging techniques; if a sample is placed in a non-uniform magnetic field then the resonance frequencies of the sample's nuclei depend on where in the field they are located. Since the resolution of the imaging technique depends on the magnitude of magnetic field gradient, many efforts are made to develop increased field strength, often using superconductors. The effectiveness of NMR can also be improved using hyperpolarization, and/or using two-dimensional, three-dimensional and higher-dimensional multi-frequency techniques.



First 1 GHz NMR Spectrometer (1000 MHz, 23.5 T) was installed at the new 'Centre de RMN à Très Hauts Champs' in Lyon, France in August 2009



Pacific Northwest National Laboratory's high magnetic field (800 MHz, 18.8 T) NMR spectrometer.

The principle of NMR usually involves two sequential steps:

- The alignment (polarization) of the magnetic nuclear spins in an applied, constant magnetic field $\mathbf{H}_0$.
- The perturbation of this alignment of the nuclear spins by employing an electro-magnetic, usually radio frequency (RF) pulse. The required perturbing frequency is dependent upon the static magnetic field ($\mathbf{H}_0$) and the nuclei of observation.

The two fields are usually chosen to be perpendicular to each other as this maximizes the NMR signal strength. The resulting response by the total magnetization ($\mathbf{M}$) of the nuclear spins is the phenomenon that is exploited in NMR spectroscopy and magnetic resonance imaging. Both use intense applied magnetic fields ($\mathbf{H}_0$) in order to achieve dispersion and very high stability to deliver spectral resolution, the details of which are described by chemical shifts, the Zeeman effect, and Knight shifts (in metals).

NMR phenomena are also utilized in low-field NMR, NMR spectroscopy and MRI in the Earth's magnetic field (referred to as Earth's field NMR), and in several types of magnetometers.

History

Nuclear magnetic resonance was first described and measured in molecular beams by Isidor Rabi in 1938,^[1] and in 1944, Rabi was awarded the Nobel Prize in physics for this work.^[2] In 1946, Felix Bloch and Edward Mills Purcell expanded the technique for use on liquids and solids, for which they shared the Nobel Prize in physics in 1952.^[3]

Purcell had worked on the development and radar applications during World War II at Massachusetts Institute of Technology's Radiation Laboratory. His work during that project on the production and detection of RF energy, and on the absorption of such RF energy by matter, preceded his discovery of NMR.

They noticed that magnetic nuclei, like ^1H and ^{31}P , could absorb RF energy when placed in a magnetic field of a strength specific to the identity of the nuclei. When this absorption occurs, the nucleus is described as being *in resonance*. Different atomic nuclei within a molecule resonate at different (radio) frequencies for the same magnetic field strength. The observation of such magnetic resonance frequencies of the nuclei present in a molecule allows any trained user to discover essential, chemical and structural information about the molecule.

The development of nuclear magnetic resonance as a technique of analytical chemistry and biochemistry parallels the development of electromagnetic technology and its introduction into civilian use.

Theory of nuclear magnetic resonance

Nuclear spin and magnets

All nucleons, that is neutrons and protons, composing any atomic nucleus, have the intrinsic quantum property of spin. The overall spin of the nucleus is determined by the spin quantum number S . If the number of both the protons and neutrons in a given nuclide are even then $S = 0$, i.e. there is no overall spin; just as electrons pair up in atomic orbitals, so do even numbers of protons or even numbers of neutrons (which are also spin- $\frac{1}{2}$ particles and hence fermions) pair up giving zero overall spin.

However, a proton and neutron will have lower energy when their spins are parallel, **not anti-parallel**, as this parallel spin alignment does not infringe upon the Pauli principle, but instead has to do with the quark structure of these two nucleons. Therefore, the spin ground state for the deuteron (the deuterium nucleus, or the ^2H isotope of hydrogen)—that has only a proton and a neutron—corresponds to a spin value of **1**, *not of zero*; the single, isolated deuteron is therefore exhibiting an NMR absorption spectrum characteristic of a quadrupolar nucleus of spin **1**, which in the 'rigid' state at very low temperatures is a characteristic ('Pake') *doublet*, (not a singlet as for a single, isolated ^1H , or any other isolated fermion or dipolar nucleus of spin $1/2$). On the other hand, because of the Pauli principle, the (radioactive) tritium isotope has to have a pair of anti-parallel spin neutrons (of total spin zero for the neutron spin couple), plus a proton of spin $1/2$; therefore, the character of the tritium nucleus ('triton') is again

magnetic dipolar, *not quadrupolar*—like its non-radioactive deuteron neighbor—and the tritium nucleus total spin value is again $1/2$, just like for the simpler, abundant hydrogen isotope, ^1H nucleus (the *proton*). The NMR absorption (radio) frequency for tritium is however slightly higher than that of ^1H because the tritium nucleus has a slightly higher gyromagnetic ratio than ^1H . In many other cases of *non-radioactive* nuclei, the overall spin is also non-zero. For example, the ^{27}Al nucleus has an overall spin value $S = 5/2$.

A non-zero spin is thus always associated with a non-zero magnetic moment (μ) via the relation $\mu = \gamma S$, where γ is the gyromagnetic ratio. It is this magnetic moment that allows the observation of NMR absorption spectra caused by transitions between nuclear spin levels. Most nuclides (with some rare exceptions) that have both even numbers of protons and even numbers of neutrons, also have zero nuclear magnetic moments—and also have zero magnetic dipole and quadrupole moments; therefore, such nuclides do not exhibit any NMR absorption spectra. Thus, ^{18}O is an example of a nuclide that has no NMR absorption, whereas ^{13}C , ^{31}P , ^{35}Cl and ^{37}Cl are nuclides that do exhibit NMR absorption spectra; the last two nuclei are quadrupolar nuclei whereas the preceding two nuclei (^{13}C and ^{31}P) are dipolar ones.

Electron spin resonance (ESR) is a related technique which detects transitions between electron spin levels instead of nuclear ones. The basic principles are similar; however, the instrumentation, data analysis and detailed theory are significantly different. Moreover, there is a much smaller number of molecules and materials with unpaired electron spins that exhibit ESR (or electron paramagnetic resonance (EPR)) absorption than those that have NMR absorption spectra. Significantly also, is the much greater sensitivity of ESR and EPR in comparison with NMR. Furthermore, ferromagnetic materials and thin films may exhibit 'very unusual', highly resolved ferromagnetic resonance (FMR) spectra, or ferromagnetic spin wave resonance (FSWR) excitations in non-crystalline solids such as ferromagnetic metallic glasses, well beyond the common single-transitions of most routine NMR, FMR and EPR studies.^{[4] [5]}

Values of spin angular momentum

The angular momentum associated with nuclear spin is quantized. This means both that the magnitude of angular momentum is quantized (i.e. S can only take on a restricted range of values), and also that the orientation of the associated angular momentum is quantized. The associated quantum number is known as the magnetic quantum number, m , and can take values from $+S$ to $-S$, in integer steps. Hence for any given nucleus, there is a total of $2S + 1$ angular momentum states.

The z-component of the angular momentum vector ($\mathbf{S}$) is therefore $S_z = m\hbar$, where $\hbar$ is the reduced Planck constant. The z-component of the magnetic moment is simply:

$$\mu_z = \gamma S_z = \gamma m\hbar$$

Spin behavior in a magnetic field

Consider nuclei which have a spin of one-half, like ^1H , ^{13}C or ^{19}F . The nucleus has two possible spin states: $m = \frac{1}{2}$ or $m = -\frac{1}{2}$ (also referred to as spin-up and spin-down, or sometimes α and β spin states, respectively). These states are degenerate, that is they have the same energy. Hence the number of atoms in these two states will be approximately equal at thermal equilibrium.

If a nucleus is placed in a magnetic field, however, the interaction between the nuclear magnetic moment and the external magnetic field mean the two states no longer have the same energy. The energy of a magnetic moment μ when in a magnetic field $\mathbf{B}_0$ is given by:

$$E = -\mu \cdot \mathbf{B}_0 = -\mu_x B_{0x} - \mu_y B_{0y} - \mu_z B_{0z}.$$

Usually the z axis is chosen to be along $\mathbf{B}_0$, and the above expression reduces to:

$$E = -\mu_z B_0,$$

or alternatively:

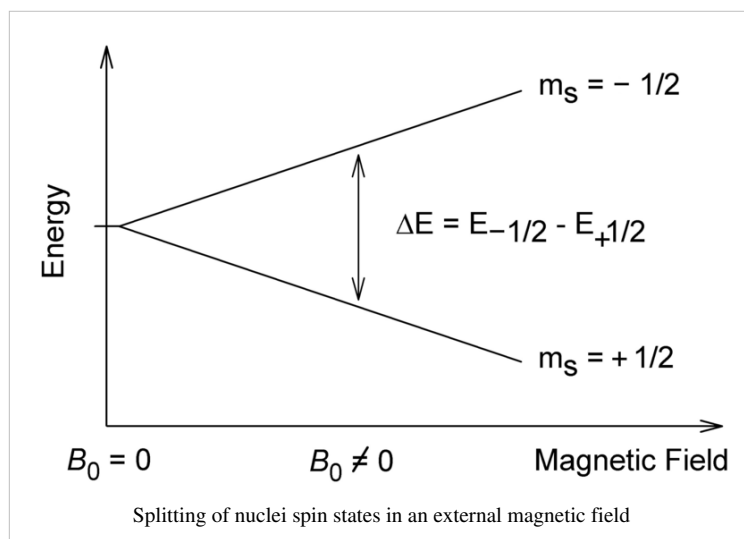
$$E = -\gamma \hbar m B_0.$$

As a result the different nuclear spin states have different energies in a non-zero magnetic field. In hand-waving terms, we can talk about the two spin states of a spin $\frac{1}{2}$ as being *aligned* either with or against the magnetic field. If γ is positive (true for most isotopes) then $m = \frac{1}{2}$ is the lower energy state.

The energy difference between the two states is:

$$\Delta E = \gamma \hbar B_0,$$

and this difference results in a small population bias toward the lower energy state.



Magnetic resonance by nuclei

Resonant absorption by nuclear spins will occur only when electromagnetic radiation of the correct frequency (e.g., equaling the Larmor precession rate) is being applied to match the energy difference between the nuclear spin levels in a constant magnetic field of the appropriate strength. The energy of an absorbed photon is then $E = h\nu_0$, where ν_0 is the resonance radiofrequency that has to match (that is, it has to be equal to) the Larmor precession frequency ν_L of the nuclear magnetization in the constant magnetic field $\mathbf{B}_0$. Hence, a magnetic resonance absorption will only occur when $\Delta E = h\nu_0$, which is when $\nu_0 = \gamma B_0 / (2\pi)$. Such magnetic resonance frequencies typically correspond to the radio frequency (or RF) range of the electromagnetic spectrum for magnetic fields up to ~ 20 T. It is this magnetic resonant absorption which is detected in NMR.

Nuclear shielding

It might appear from the above that all nuclei of the same nuclide (and hence the same g) would resonate at the same frequency. This is not the case. The most important perturbation of the NMR frequency for applications of NMR is the 'shielding' effect of the surrounding electrons. In general, this electronic shielding reduces the magnetic field *at the nucleus* (which is what determines the NMR frequency).

As a result the energy gap is reduced, and the frequency required to achieve resonance is also reduced. This shift in the NMR frequency due to the electrons' molecular orbital coupling to the external magnetic field is called chemical shift, and it explains why NMR is able to probe the chemical structure of molecules which depends on the electron density distribution in the corresponding molecular orbitals. If a nucleus in a specific chemical group is shielded to a higher degree by a higher electron density of its surrounding molecular orbital, then its NMR frequency will be shifted "upfield" (that is, a lower chemical shift), whereas if it is less shielded by such surrounding electron density, then its NMR frequency will be shifted "downfield" (that is, a higher chemical shift).

Unless the local symmetry of such molecular orbitals is very high (leading to "isotropic" shift), the shielding effect will depend on the orientation of the molecule with respect to the external field ($\mathbf{B}_0$). In solid-state NMR spectroscopy, magic angle spinning is required to average out this orientation dependence in order to obtain values close to the average chemical shifts. This is unnecessary in conventional NMR investigations of molecules, since rapid molecular tumbling averages out the chemical shift anisotropy (CSA). In this case, the term "average" chemical shift (ACS) is used.

Relaxation

The process called population relaxation refers to nuclei that return to the thermodynamic state in the magnet. This process is also called T_1 , "spin-lattice" or "longitudinal magnetic" relaxation, where T_1 refers to the mean time for an individual nucleus to return to its thermal equilibrium state of the spins. Once the nuclear spin population is relaxed, it can be probed again, since it is in the initial, equilibrium (mixed) state.

The precessing nuclei can also fall out of alignment with each other (returning the net magnetization vector to a non-precessing field) and stop producing a signal. This is called T_2 or *transverse relaxation*. Because of the difference in the actual relaxation mechanisms involved (for example, inter-molecular vs. intra-molecular magnetic dipole-dipole interactions), T_1 is always longer than T_2 (that is, slower spin-lattice relaxation, for example because of smaller dipole-dipole interaction effects). In practice, the value of T_2^* which is the actually observed decay time of the observed NMR signal, or free induction decay, (to 1/e of the initial amplitude immediately after the resonant RF pulse)-- also depends on the static magnetic field inhomogeneity, which is quite significant. (There is also a smaller but significant contribution to the observed FID shortening from the RF inhomogeneity of the resonant pulse). In the corresponding FT-NMR spectrum—meaning the Fourier transform of the free induction decay--the T_2^* time is inversely related to the width of the NMR signal in frequency units. Thus, a nucleus with a long T_2 relaxation time gives rise to a very sharp NMR peak in the FT-NMR spectrum for a very homogeneous ("well-shimmed") static magnetic field, whereas nuclei with shorter T_2 values give rise to broad FT-NMR peaks even when the magnet is shimmed well. Both T_1 and T_2 depend on the rate of molecular motions as well as the gyromagnetic ratios of both the resonating and their strongly interacting, next-neighbor nuclei that are not at resonance.

NMR spectroscopy

NMR spectroscopy is one of the principal techniques used to obtain physical, chemical, electronic and structural information about molecules due to either the chemical shift, Zeeman effect, or the Knight shift effect, or a combination of both, on the resonant frequencies of the nuclei present in the sample. It is a powerful technique that can provide detailed information on the topology, dynamics and three-dimensional structure of molecules in solution and the solid state. Thus, structural and dynamic information is obtainable (with or without "magic angle" spinning (MAS)) from NMR studies of quadrupolar nuclei (that is, those nuclei with spin $S > \frac{1}{2}$) even in the presence of magnetic dipole-dipole interaction broadening (or simply, dipolar broadening) which is always much smaller than the quadrupolar interaction strength because it is a magnetic vs. an electric interaction effect.

Additional structural and chemical information may be obtained by performing double-quantum NMR experiments for quadrupolar nuclei such as ^2H .

Also, nuclear magnetic resonance is one of the techniques that has been used to design quantum automata, and also build elementary quantum computers.^{[6] [7]}



900 MHz, 21.2 T NMR Magnet at HWB-NMR, Birmingham, UK

Continuous wave (CW) spectroscopy

In its first few decades, nuclear magnetic resonance spectrometers used a technique known as continuous-wave spectroscopy (CW spectroscopy). Although NMR spectra could be, and have been, obtained using a fixed magnetic field and sweeping the frequency of the electromagnetic radiation, this more typically involved using a fixed frequency source and varying the current (and hence magnetic field) in an electromagnet to observe the resonant absorption signals. This is the origin of the counterintuitive, but still common, "high" and "low" field terminology for low frequency and high frequency regions respectively of the NMR spectrum.

CW spectroscopy is inefficient in comparison to Fourier techniques (see below) as it probes the NMR response at individual frequencies in succession. As the NMR signal is intrinsically weak, the observed spectra suffer from a poor signal-to-noise ratio. This can be mitigated by signal averaging i.e. adding the spectra from repeated measurements. While the NMR signal is constant between scans and so adds linearly, the random noise adds more slowly—as the square-root of the number of spectra (see Random walk). Hence the overall ratio of the signal to the noise increases as the square-root of the number of spectra measured.

Fourier transform spectroscopy

Most applications of NMR involve full NMR spectra, that is, the intensity of the NMR signal as a function of frequency. Early attempts to acquire the NMR spectrum more efficiently than simple CW methods involved irradiating simultaneously with more than one frequency. A revolution in NMR occurred when short pulses of radio-frequency were used (centered at the middle of the NMR spectrum). In simple terms, a short square pulse of a given "carrier" frequency "contains" a range of frequencies centered about the carrier frequency, with the range of excitation (bandwidth) being inversely proportional to the pulse duration (the Fourier transform (FT) of an approximate square wave contains contributions from all the frequencies in the neighborhood of the principal frequency). The restricted range of the NMR frequencies made it relatively easy to use short (millisecond to microsecond) radiofrequency (RF) pulses to excite the entire NMR spectrum.

Applying such a pulse to a set of nuclear spins simultaneously excites all the single-quantum NMR transitions. In terms of the net magnetization vector, this corresponds to tilting the magnetization vector away from its equilibrium position (aligned along the external magnetic field). The out-of-equilibrium magnetization vector precesses about the external magnetic field vector at the NMR frequency of the spins. This oscillating magnetization vector induces a current in a nearby pickup coil, creating an electrical signal oscillating at the NMR frequency. This signal is known as the free induction decay (FID) and contains the vector-sum of the NMR responses from all the excited spins. In order to obtain the frequency-domain NMR spectrum (NMR absorption intensity vs. NMR frequency) this time-domain signal (intensity vs. time) must be FTed. Fortunately the development of FT NMR coincided with the development of digital computers and Fast Fourier Transform algorithms. FT methods can be applied to many types of spectroscopy; see the general article on Fourier transform spectroscopy.

Richard R. Ernst was one of the pioneers of pulse (FT) NMR and won a Nobel Prize in chemistry in 1991 for his work on FT NMR and his development of multi-dimensional NMR (see below).

Multi-dimensional NMR Spectroscopy

The use of pulses of different shapes, frequencies and durations in specifically-designed patterns or *pulse sequences* allows the spectroscopist to extract many different types of information about the molecule. Multi-dimensional nuclear magnetic resonance spectroscopy is a kind of FT NMR in which there are at least two pulses and, as the experiment is repeated, the pulse sequence is varied. In *multidimensional nuclear magnetic resonance* there will be a sequence of pulses and, at least, one variable time period. In three dimensions, two time sequences will be varied. In four dimensions, three will be varied.

There are many such experiments. In one, these time intervals allow (amongst other things) magnetization transfer between nuclei and, therefore, the detection of the kinds of nuclear-nuclear interactions that allowed for the magnetization transfer. Interactions that can be detected are usually classified into two kinds. There are *through-bond* interactions and *through-space* interactions, the latter usually being a consequence of the nuclear Overhauser effect. Experiments of the nuclear Overhauser variety may be employed to establish distances between atoms, as for example by 2D-FT NMR of molecules in solution.

Although the fundamental concept of 2D-FT NMR was proposed by Jean Jeener from the Free University of Brussels at an International Conference, this idea was largely developed by Richard Ernst who won the 1991 Nobel prize in Chemistry for his work in FT NMR, including multi-dimensional FT NMR, and especially 2D-FT NMR of small molecules.^[8] Multi-dimensional FT NMR experiments were then further developed into powerful methodologies for studying biomolecules in solution, in particular for the determination of the structure of biopolymers such as proteins or even small nucleic acids.^[9]

Kurt Wüthrich shared (with John B. Fenn) in 2002 the Nobel Prize in Chemistry for his work in protein FT NMR in solution.

Solid-state NMR spectroscopy

This technique complements biopolymer X-ray crystallography in that it is frequently applicable to biomolecules in a liquid or liquid crystal phase, whereas crystallography, as the name implies, is performed on molecules in a solid phase. Though nuclear magnetic resonance is used to study solids, extensive atomic-level biomolecular structural detail is especially challenging to obtain in the solid state. There is little signal averaging by thermal motion in the solid state, where most molecules can only undergo restricted vibrations and rotations at room temperature, each in a slightly different electronic environment, therefore exhibiting a different NMR absorption peak. Such a variation in the electronic environment of the resonating nuclei results in a blurring of the observed spectra—which is often only a broad Gaussian band for non-quadrupolar spins in a solid—thus making the interpretation of such "dipolar" and "chemical shift anisotropy" (CSA) broadened spectra either very difficult or impossible.

Professor Raymond Andrew at Nottingham University in the UK pioneered the development of high-resolution solid-state nuclear magnetic resonance. He was the first to report the introduction of the MAS (magic angle sample spinning; MASS) technique that allowed him to achieve spectral resolution in solids sufficient to distinguish between chemical groups with either different chemical shifts or distinct Knight shifts. In MASS, the sample is spun at several kilohertz around an axis that makes the so-called magic angle θ_m (which is $\sim 54.74^\circ$, where $\cos^2\theta_m = 1/3$) with respect to the direction of the static magnetic field $\mathbf{B}_0$; as a result of such magic angle sample spinning, the chemical shift anisotropy bands are averaged to their corresponding average (isotropic) chemical shift values. The above expression involving $\cos^2\theta_m$ has its origin in a calculation that predicts the magnetic dipolar interaction effects to cancel out for the specific value of θ_m called the magic angle. One notes that correct alignment of the sample rotation axis as close as possible to θ_m is essential for cancelling out the dipolar interactions whose strength for angles sufficiently far from θ_m is usually greater than ~ 10 kHz for C-H bonds in solids, for example, and it is thus greater than their CSA values.

There are different angles for the sample spinning relative to the applied field for the averaging of quadrupole interactions and paramagnetic interactions, correspondingly $\sim 30.6^\circ$ and $\sim 70.1^\circ$.

A concept developed by Sven Hartmann and Erwin Hahn was utilized in transferring magnetization from protons to less sensitive nuclei (popularly known as cross-polarization) by M.G. Gibby, Alex Pines and John S. Waugh. Then, Jake Schaefer and Ed Stejskal demonstrated also the powerful use of cross-polarization under MASS conditions which is now routinely employed to detect low-abundance and low-sensitivity nuclei.

Sensitivity

Because the intensity of nuclear magnetic resonance signals and, hence, the sensitivity of the technique depends on the strength of the magnetic field the technique has also advanced over the decades with the development of more powerful magnets. Advances made in audio-visual technology have also improved the signal-generation and processing capabilities of newer machines.

As noted above, the sensitivity of nuclear magnetic resonance signals is also dependent on the presence of a magnetically-susceptible nuclide and, therefore, either on the natural abundance of such nuclides or on the ability of the experimentalist to artificially enrich the molecules, under study, with such nuclides. The most abundant naturally-occurring isotopes of hydrogen and phosphorus (for example) are both magnetically susceptible and readily useful for nuclear magnetic resonance spectroscopy. In contrast, carbon and nitrogen have useful isotopes but which occur only in very low natural abundance.

Other limitations on sensitivity arise from the quantum-mechanical nature of the phenomenon. For quantum states separated by energy equivalent to radio frequencies, thermal energy from the environment causes the populations of the states to be close to equal. Since incoming radiation is equally likely to cause stimulated emission (a transition from the upper to the lower state) as absorption, the NMR effect depends on an excess of nuclei in the lower states. Several factors can reduce sensitivity, including

- Increasing temperature, which evens out the population of states. Conversely, low temperature NMR can sometimes yield better results than room-temperature NMR, providing the sample remains liquid.
- Saturation of the sample with energy applied at the resonant radiofrequency. This manifests in both CW and pulsed NMR; in the first, CW, case this happens by using too much continuous power that keeps the upper spin levels completely populated; in the second case, saturation occurs by pulsing too frequently—without allowing time for the nuclei to return to thermal equilibrium through spin-lattice relaxation. For nuclei such as ^{29}Si this is a serious practical problem as the relaxation time is measured in seconds; for protons in "pure" ice, or ^{19}F in high-purity (undoped) LiF crystals the spin-lattice relaxation time can be on the order of an hour or longer. The use of shorter RF pulses that tip the magnetization by less than 90° can partially solve the problem by allowing spectral acquisition without the complete loss of NMR signal.
- Non-magnetic effects, such as electric-quadrupole coupling of spin-1 and spin- $\frac{3}{2}$ nuclei with their local environment, which broaden and weaken absorption peaks. ^{14}N , an abundant spin-1 nucleus, is difficult to study for this reason. High resolution NMR instead probes molecules using the rarer ^{15}N isotope, which has spin- $\frac{1}{2}$.

Isotopes

Many chemical elements can be used for NMR analysis.^[10]

Commonly used nuclei:

- ^1H , the most commonly used spin $\frac{1}{2}$ nucleus in NMR investigation, has been studied using many forms of NMR. Hydrogen is highly abundant, especially in biological systems. It is the nucleus most sensitive to NMR signal (apart from ^3H which is not commonly used due to its instability and radioactivity). Proton NMR produces narrow chemical shift with sharp signals. The ^1H signal has been the sole diagnostic nucleus used for clinical magnetic resonance imaging.
- ^2H , a spin 1 nucleus commonly utilized as signal-free medium in the form of deuterated solvents during proton NMR, to avoid signal interference from hydrogen-containing solvents in measurement of ^1H solutes. Also used in determining the behavior of lipids in lipid membranes and other solids or liquid crystals as it is a relatively non-perturbing label which can selectively replace ^1H . Alternatively, ^2H can be detected in media specially labeled with ^2H . Deuterium resonance is commonly used in high-resolution NMR spectroscopy to monitor drifts in the magnetic field strength (lock) and to improve the homogeneity of the external magnetic field.
- ^3He , is very sensitive to NMR. There is a very low percentage in natural helium, and subsequently has to be purified from ^4He . It is used mainly in studies of endohedral fullerenes, where its chemical inertness is beneficial to ascertaining the structure of the entrapping fullerene.
- ^{10}B , lower sensitivity than ^{11}B . Quartz tubes must be used as borosilicate glass interferes with measurement.
- ^{11}B , more sensitive than ^{10}B , yields sharper signals. Quartz tubes must be used as borosilicate glass interferes with measurement.
- ^{13}C spin- $\frac{1}{2}$, is widely used, despite its relative paucity in naturally-occurring carbon (approximately 1%). It is stable to nuclear decay. Since there is a low percentage in natural carbon, spectrum acquisition on samples which have not been experimentally enriched in ^{13}C takes a long time. Frequently used for labeling of compounds in synthetic and metabolic studies. Has low sensitivity and wide chemical shift, yields sharp signals. Low percentage makes it useful by preventing spin-spin couplings and makes the spectrum appear less crowded. Slow relaxation means that spectra are not integrable unless long acquisition times are used.
- ^{14}N , spin-1, medium sensitivity nucleus with wide chemical shift. Its large quadrupole moment interferes in acquisition of high resolution spectra, limiting usefulness to smaller molecules and functional groups with a high degree of symmetry such as the headgroups of lipids.
- ^{15}N , spin- $\frac{1}{2}$, relatively commonly used. Can be used for labeling compounds. Nucleus very insensitive but yields sharp signals. Low percentage in natural nitrogen together with low sensitivity requires high concentrations or expensive isotope enrichment.

- ^{17}O , spin-5/2, low sensitivity and very low natural abundance (0.037%), wide chemical shifts range (up to 2000 ppm). Quadrupole moment causing a line broadening. Used in metabolic and biochemical studies in studies of chemical equilibria.
- ^{19}F , spin-1/2, relatively commonly measured. Sensitive, yields sharp signals, has wide chemical shift.
- ^{31}P , spin-1/2, 100% of natural phosphorus. Medium sensitivity, wide chemical shifts range, yields sharp lines. Used in biochemical studies.
- ^{35}Cl and ^{37}Cl , broad signal. ^{35}Cl significantly more sensitive, preferred over ^{37}Cl despite its slightly broader signal. Organic chlorides yield very broad signals, its use is limited to inorganic and ionic chlorides and very small organic molecules.
- ^{43}Ca , used in biochemistry to study calcium binding to DNA, proteins, etc. Moderately sensitive, very low natural abundance.
- ^{195}Pt , used in studies of catalysts and complexes.

Other nuclei (usually used in the studies of their complexes and chemical binding, or to detect presence of the element):

- ^6Li , ^7Li
- ^9Be
- ^{19}F
- ^{21}Ne
- ^{23}Na
- ^{25}Mg
- ^{27}Al
- ^{29}Si
- ^{31}P
- ^{33}S
- ^{39}K , ^{40}K , ^{41}K
- ^{45}Sc
- ^{47}Ti , ^{49}Ti
- ^{50}V , ^{51}V
- ^{53}Cr
- ^{55}Mn
- ^{57}Fe
- ^{59}Co
- ^{61}Ni
- ^{63}Cu , ^{65}Cu
- ^{67}Zn
- ^{69}Ga , ^{71}Ga
- ^{73}Ge
- ^{77}Se
- ^{81}Br
- ^{87}Rb
- ^{87}Sr
- ^{95}Mo
- ^{109}Ag
- ^{113}Cd
- ^{119}Sn
- ^{125}Te
- ^{127}I

- ^{133}Cs
- ^{135}Ba , ^{137}Ba
- ^{139}La
- ^{183}W
- ^{199}Hg

Applications

Medicine

The application of nuclear magnetic resonance best known to the general public is magnetic resonance imaging for medical diagnosis and MR Microscopy in research settings, however, it is also widely used in chemical studies, notably in NMR spectroscopy such as proton NMR, carbon-13 NMR, deuterium NMR and phosphorus-31 NMR. Biochemical information can also be obtained from living tissue (e.g. human brain tumors) with the technique known as *in vivo* magnetic resonance spectroscopy or chemical shift NMR Microscopy.

These studies are possible because nuclei are surrounded by orbiting electrons, which are charged particles that generate small, local magnetic fields that add to or subtract from the external magnetic field, and so will partially shield the nuclei. The amount of shielding depends on the exact local environment. For example, a hydrogen bonded to an oxygen will be shielded differently than a hydrogen bonded to a carbon atom. In addition, two hydrogen nuclei can interact via a process known as spin-spin coupling, if they are on the same molecule, which will split the lines of the spectra in a recognizable way.

As one of the two major spectroscopic techniques used in metabolomics, NMR is used to generate metabolic fingerprints from biological fluids to obtain information about disease states or toxic insults.

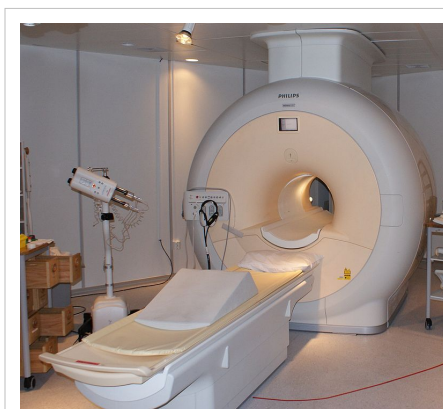
Chemistry

By studying the peaks of nuclear magnetic resonance spectra, chemists can determine the structure of many compounds. It can be a very selective technique, distinguishing among many atoms within a molecule or collection of molecules of the same type but which differ only in terms of their local chemical environment. See the articles on carbon-13 NMR and proton NMR for detailed discussions.

By studying T_2^* information, a chemist can determine the identity of a compound by comparing the observed nuclear precession frequencies to known frequencies. Further structural data can be elucidated by observing *spin-spin coupling*, a process by which the precession frequency of a nucleus can be influenced by the magnetization transfer from nearby nuclei. Spin-spin coupling is most commonly observed in NMR involving common isotopes, such as Hydrogen-1 (^1H NMR).

Because the nuclear magnetic resonance *timescale* is rather slow, compared to other spectroscopic methods, changing the temperature of a T_2^* experiment can also give information about fast reactions, such as the Cope rearrangement or about structural dynamics, such as ring-flipping in cyclohexane. At low enough temperatures, a distinction can be made between the axial and equatorial hydrogens in cyclohexane.

An example of nuclear magnetic resonance being used in the determination of a structure is that of buckminsterfullerene (often called "buckyballs", composition C_{60}). This now famous form of carbon has 60 carbon atoms forming a sphere. The carbon atoms are all in identical environments and so should see the same internal H field. Unfortunately, buckminsterfullerene contains no hydrogen and so ^{13}C nuclear magnetic resonance has to be



Medical MRI

used. ^{13}C spectra require longer acquisition times since carbon-13 is not the common isotope of carbon (unlike hydrogen, where ^1H is the common isotope). However, in 1990 the spectrum was obtained by R. Taylor and co-workers at the University of Sussex and was found to contain a single peak, confirming the unusual structure of buckminsterfullerene.^[11]

Non-destructive testing

Nuclear magnetic resonance is extremely useful for analyzing samples non-destructively. Radio waves and static magnetic fields easily penetrate many types of matter and anything that is not inherently ferromagnetic. For example, various expensive biological samples, such as nucleic acids, including RNA and DNA, or proteins, can be studied using nuclear magnetic resonance for weeks or months before using destructive biochemical experiments. This also makes nuclear magnetic resonance a good choice for analyzing dangerous samples.

Acquisition of dynamic information

In addition to providing static information on molecules by determining their 3D structures in solution, one of the remarkable advantages of NMR over X-ray crystallography is that it can be used to obtain important dynamic information including the low-frequency collective motion in proteins and DNA, for example in the Ca^{2+} -calmodulin system.^[12] The low-frequency internal motion in biomacromolecules and its biological functions have been discussed by Chou.^[13]

Data acquisition in the petroleum industry

Another use for nuclear magnetic resonance is data acquisition in the petroleum industry for petroleum and natural gas exploration and recovery. A borehole is drilled into rock and sedimentary strata into which nuclear magnetic resonance logging equipment is lowered. Nuclear magnetic resonance analysis of these boreholes is used to measure rock porosity, estimate permeability from pore size distribution and identify pore fluids (water, oil and gas). These instruments are typically low field NMR spectrometers.

Flow probes for NMR spectroscopy

Recently, real-time applications of NMR in liquid media have been developed using specifically designed flow probes (flow cell assemblies) which can replace standard tube probes. This has enabled techniques that can incorporate the use of high performance liquid chromatography (HPLC) or other continuous flow sample introduction devices.^[14]

Process control

NMR has now entered the arena of real-time process control and process optimization in oil refineries and petrochemical plants. Two different types of NMR analysis are utilized to provide real time analysis of feeds and products in order to control and optimize unit operations. Time-domain NMR (TD-NMR) spectrometers operating at low field (2–20 MHz for ^1H) yield free induction decay data that can be used to determine absolute hydrogen content values, rheological information, and component composition. These spectrometers are used in mining, polymer production, cosmetics and food manufacturing as well as coal analysis. High resolution FT-NMR spectrometers operating in the 60 MHz range with shielded permanent magnet systems yield high resolution ^1H NMR spectra of refinery and petrochemical streams. The variation observed in these spectra with changing physical and chemical properties is modeled using chemometrics to yield predictions on unknown samples. The prediction results are provided to control systems via analogue or digital outputs from the spectrometer.

Earth's field NMR

In the Earth's magnetic field, NMR frequencies are in the audio frequency range, or the very low frequency band of the radio frequency spectrum. Earth's field NMR (EFNMR) is typically stimulated by applying a relatively strong dc magnetic field pulse to the sample and, following the pulse, analyzing the resulting low frequency alternating magnetic field that occurs in the Earth's magnetic field due to free induction decay (FID). These effects are exploited in some types of magnetometers, EFNMR spectrometers, and MRI imagers. Their inexpensive portable nature makes these instruments valuable for field use and for teaching the principles of NMR and MRI.

Quantum computing

NMR quantum computing uses the spin states of molecules as qubits. NMR differs from other implementations of quantum computers in that it uses an ensemble of systems, in this case molecules. The ensemble is initialized to be the thermal equilibrium state (see quantum statistical mechanics).

Magnetometers

Various magnetometers use NMR effects to measure magnetic fields, including proton precession magnetometers (PPM) (also known as proton magnetometers), and Overhauser magnetometers. See also Earth's field NMR.

Makers of NMR equipment

Major NMR instrument makers include Oxford Instruments, Bruker, Spinlock SRL, General Electric, JEOL, Kimble Chase, Philips, Siemens AG and Varian, Inc..

Notes

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External links

Tutorial

- NMR/MRI tutorial (<http://www.cis.rit.edu/htbooks/nmr/inside.htm>)
- NMR Library (<http://nmr.chinanmr.cn/guide/eNMR/eNMRindex.html>) NMR Concepts
- NMR Course Notes (<http://www.grandinetti.org/Teaching/Chem824/NMRNotes>)

Animations and Simulations

- This animation shows a spin, the modification of spin with magnetic field and HF pulse, spin echo sequences, inversion recovery sequence, gradient echo sequence and relaxation of spin (http://www.bigs.de/BLH/en/index.php?option=com_content&view=category&layout=blog&id=51&Itemid=222)
- Animation of NMR spin $\frac{1}{2}$ precession (<http://www.chem.queensu.ca/FACILITIES/NMR/nmr/webcourse/precess.htm>)
- A free interactive simulation of NMR principles (<http://vam.anest.ufl.edu/forensic/nmr.html>)

Video

- introduction to NMR and MRI (<http://www.youtube.com/watch?v=7aRKAXD4dAg>)
- Richard Ernst, NL - Developer of Multidimensional NMR techniques (<http://www.vega.org.uk/video/programme/21>) Freeview video provided by the Vega Science Trust.
- 'An Interview with Kurt Wuthrich' (<http://www.vega.org.uk/video/programme/115>) Freeview video by the Vega Science Trust (Wüthrich was awarded a Nobel Prize in Chemistry in 2002 "for his development of nuclear magnetic resonance spectroscopy for determining the three-dimensional structure of biological macromolecules in solution").

2D-FT NMRI and Spectroscopy

2D-FT Nuclear Magnetic resonance imaging (2D-FT NMRI), or **Two-dimensional Fourier transform** magnetic resonance imaging (NMRI), is primarily a non-invasive imaging technique most commonly used in biomedical research and medical radiology/nuclear medicine/MRI to visualize structures and functions of the living systems and single cells. For example it can provides fairly detailed images of a human body in any selected cross-sectional plane, such as longitudinal, transversal, sagital, etc. NMRI provides much greater contrast especially for the different soft tissues of the body than computed tomography (CT) as its most sensitive option observes the nuclear spin distribution and dynamics of highly mobile molecules that contain the naturally abundant, stable hydrogen isotope ^1H as in plasma water molecules, blood, disolved metabolites and fats. This approach makes it most useful in cardiovascular, oncological (cancer), neurological (brain), musculoskeletal, and cartilage imaging. Unlike CT, it uses no ionizing radiation, and also unlike nuclear imaging it does not employ any radioactive isotopes. Some of the first MRI images reported were published in 1973^[1] and the first study performed on a human took place on July 3, 1977.^[2] Earlier papers were also published by Peter Mansfield^[3] in UK (Nobel Laureate in 2003), and R. Damadian in the USA, (together with an approved patent for magnetic imaging). Unpublished 'high-resolution' (50 micron resolution) images of other living systems, such as hydrated wheat grains, were obtained and communicated in UK in 1977-1979, and were subsequently confirmed by articles published in *Nature*.

NMRI Principle

Certain nuclei such as ^1H nuclei, or 'fermions' have spin-1/2, because there are two spin states, referred to as "up" and "down" states. The nuclear magnetic resonance absorption phenomenon occurs when samples containing such nuclear spins are placed in a static magnetic field and a very short radiofrequency pulse is applied with a center, or carrier, frequency matching that of the transition between the up and down states of the spin-1/2 ^1H nuclei that were polarized by the static magnetic field.^[4] Very low field schemes have also been recently reported.^[5]



Advanced clinical diagnostics and biomedical research NMR Imaging instrument.

Chemical Shifts

NMR is a very useful family of techniques for chemical and biochemical research because of the chemical shift; this effect consists in a frequency shift of the nuclear magnetic resonance for specific chemical groups or atoms as a result of the partial shielding of the corresponding nuclei from the applied, static external magnetic field by the electron orbitals (or molecular orbitals) surrounding such nuclei present in the chemical groups. Thus, the higher the electron density surrounding a specific nucleus the larger the chemical shift will be. The resulting magnetic field at the nucleus is thus lower than the applied external magnetic field and the resonance frequencies observed as a result of such shielding are lower than the value that would be observed in the absence of any electronic orbital shielding. Furthermore, in order to obtain a chemical shift value independent of the strength of the applied magnetic field and

allow for the direct comparison of spectra obtained at different magnetic field values, the chemical shift is defined by the ratio of the strength of the local magnetic field value at the observed (electron orbital-shielded) nucleus by the external magnetic field strength, H_{loc} / H_0 . The first NMR observations of the chemical shift, with the correct physical chemistry interpretation, were reported for ^{19}F containing compounds in the early 1950's by Herbert S. Gutowsky and Charles P. Slichter from the University of Illinois at Urbana (USA).

NMR Imaging Principles

A number of methods have been devised for combining magnetic field gradients and radiofrequency pulsed excitation to obtain an image. Two major methods involve either 2D-FT or 3D-FT^[6] reconstruction from projections, somewhat similar to Computed Tomography, with the exception of the image interpretation that in the former case must include dynamic and relaxation/contrast enhancement information as well. Other schemes involve building the NMR image either point-by-point or line-by-line. Some schemes use instead gradients in the rf field rather than in the static magnetic field. The majority of NMR images routinely obtained are either by the Two-Dimensional Fourier Transform (2D-FT) technique^[7] (with slice selection), or by the Three-Dimensional Fourier Transform (3D-FT) techniques that are however much more time consuming at present. 2D-FT NMRI is sometime called in common parlance a "spin-warp". An NMR image corresponds to a spectrum consisting of a number of 'spatial frequencies' at different locations in the sample investigated, or in a patient.^[8] A two-dimensional Fourier transformation of such a "real" image may be considered as a representation of such "real waves" by a matrix of spatial frequencies known as the k-space. We shall see next in some mathematical detail how the 2D-FT computation works to obtain 2D-FT NMR images.

Two-dimensional Fourier transform imaging and spectroscopy

A two-dimensional Fourier transform (2D-FT) is computed numerically or carried out in two stages, both involving 'standard', one-dimensional Fourier transforms. However, the second stage Fourier transform is not the inverse Fourier transform (which would result in the original function that was transformed at the first stage), but a Fourier transform in a second variable-- which is 'shifted' in value-- relative to that involved in the result of the first Fourier transform. Such 2D-FT analysis is a very powerful method for both NMRI and two-dimensional nuclear magnetic resonance spectroscopy (2D-FT NMRS)^[9] that allows the three-dimensional reconstruction of polymer and biopolymer structures at atomic resolution^[10] for molecular weights (Mw) of dissolved biopolymers in aqueous solutions (for example) up to about 50,000 Mw. For larger biopolymers or polymers, more complex methods have been developed to obtain limited structural resolution needed for partial 3D-reconstructions of higher molecular structures, e.g. for up 900,000 Mw or even oriented microcrystals in aqueous suspensions or single crystals; such methods have also been reported for *in vivo* 2D-FT NMR spectroscopic studies of algae, bacteria, yeast and certain mammalian cells, including human ones. The 2D-FT method is also widely utilized in optical spectroscopy, such as *2D-FT NIR hyperspectral imaging* (2D-FT NIR-HS), or in MRI imaging for research and clinical, diagnostic applications in Medicine. In the latter case, 2D-FT NIR-HS has recently allowed the identification of single, malignant cancer cells surrounded by healthy human breast tissue at about 1 micron resolution, well-beyond the resolution obtainable 2D-FT NMRI for such systems in the limited time available for such diagnostic investigations (and also in magnetic fields up to the FDA approved magnetic field strength H_0 of 4.7 T, as shown in the top image of the state-of-the-art NMRI instrument). A more precise mathematical definition of the 'double' (2D) Fourier transform involved in both 2D NMRI and 2D-FT NMRS is specified next, and a precise example follows this generally accepted definition.

2D-FT Definition

A 2D-FT, or two-dimensional Fourier transform, is a standard Fourier transformation of a function of two variables, $f(x_1, x_2)$, carried first in the first variable x_1 , followed by the Fourier transform in the second variable x_2 of the resulting function $F(s_1, x_2)$. Note that in the case of both 2D-FT NMRI and 2D-FT NMRS the two independent variables in this definition are in the time domain, whereas the results of the two successive Fourier transforms have, of course, frequencies as the independent variable in the NMRS, and ultimately spatial coordinates for both 2D NMRI and 2D-FT NMRS following computer structural reconstructions based on special algorithms that are different from FT or 2D-FT. Moreover, such structural algorithms are different for 2D NMRI and 2D-FT NMRS: in the former case they involve macroscopic, or anatomical structure determination, whereas in the latter case of 2D-FT NMRS the atomic structure reconstruction algorithms are based on the quantum theory of a microphysical (quantum) process such as nuclear Overhauser enhancement NOE, or specific magnetic dipole-dipole interactions^[11] between neighbor nuclei.

Example 1

A 2D Fourier transformation and phase correction is applied to a set of 2D NMR (FID) signals: $s(t_1, t_2)$ yielding a real 2D-FT NMR 'spectrum' (collection of 1D FT-NMR spectra) represented by a matrix S whose elements are

$$S(\nu_1, \nu_2) = \text{Re} \int \int \cos(\nu_1 t_1) \exp(-i\nu_2 t_2) s(t_1, t_2) dt_1 dt_2$$

where: ν_1 and ν_2 denote the discrete indirect double-quantum and single-quantum(detection) axes, respectively, in the 2D NMR experiments. Next, the covariance matrix is calculated in the frequency domain according to the following equation

$$C(\nu'_2, \nu_2) = S^T S = \sum_{\nu_1} [S(\nu_1, \nu'_2) S(\nu_1, \nu_2)], \text{ with } \nu_2, \nu'_2 \text{ taking all possible single-quantum frequency values and with the summation carried out over all discrete, double quantum frequencies } \nu_1.$$

Example 2

Atomic Structure from 2D-FT STEM Images^[12] of electron distributions in a high-temperature cuprate superconductor 'paracrystal' reveal both the domains (or 'location') and the local symmetry of the 'pseudo-gap' in the electron-pair correlation band responsible for the high-temperature superconductivity effect (obtained at Cornell University). So far there have been three Nobel prizes awarded for 2D-FT NMR/MRI during 1992-2003, and an additional, earlier Nobel prize for 2D-FT of X-ray data ('CAT scans'); recently the advanced possibilities of 2D-FT techniques in Chemistry, Physiology and Medicine^[13] received very significant recognition.^[14]

Brief explanation of NMRI diagnostic uses in Pathology

As an example, a diseased tissue such as a malignant tumor, can be detected by 2D-FT NMRI because the hydrogen nuclei of molecules in different tissues return to their equilibrium spin state at different relaxation rates, and also because of the manner in which a malignant tumor spreads and grows rapidly along the blood vessels adjacent to the tumor, also inducing further vascularization to occur. By changing the pulse delays in the RF pulse sequence employed, and/or the RF pulse sequence itself, one may obtain a 'relaxation-based contrast', or contrast enhancement between different types of body tissue, such as normal vs. diseased tissue cells for example. Excluded from such diagnostic observations by NMRI are all patients with ferromagnetic metal implants, (e.g., cochlear implants), and all cardiac pacemaker patients who cannot undergo any NMRI scan because of the very intense magnetic and RF fields employed in NMRI which would strongly interfere with the correct functioning of such pacemakers. It is, however, conceivable that future developments may also include along with the NMRI diagnostic treatments with special techniques involving applied magnetic fields and very high frequency RF. Already, surgery with special tools is being experimented on in the presence of NMR imaging of subjects. Thus, NMRI is used to

image almost every part of the body, and is especially useful for diagnosis in neurological conditions, disorders of the muscles and joints, for evaluating tumors, such as in lung or skin cancers, abnormalities in the heart (especially in children with hereditary disorders), blood vessels, CAD, atherosclerosis and cardiac infarcts ^[15] (courtesy of Dr. Robert R. Edelman)

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External links

- Cardiac Infarct or "heart attack" Imaged in Real Time by 2D-FT NMRI (http://www.mr-tip.com/exam_gifs/cardiac_infarct_short_axis_cine_6.gif)
- 3D Animation Movie about MRI Exam (<http://www.patienccys.com/MRI/>)
- Interactive Flash Animation on MRI (<http://www.e-mri.org>) - *Online Magnetic Resonance Imaging physics and technique course*
- International Society for Magnetic Resonance in Medicine (<http://www.ismrm.org>)
- Danger of objects flying into the scanner (http://www.simplyphysics.com/flying_objects.html)

Related Wikipedia websites

- Medical imaging
- Computed tomography
- Magnetic resonance microscopy
- Fourier transform spectroscopy
- FT-NIRS
- Magnetic resonance elastography
- Nuclear magnetic resonance (NMR)
- Chemical shift
- Relaxation
- Robinson oscillator
- Earth's field NMR (EFNMR)
- Rabi cycle

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EPR spectroscopy

Electron paramagnetic resonance (EPR) or **electron spin resonance** (ESR) spectroscopy is a technique for studying chemical species that have one or more unpaired electrons, such as organic and inorganic free radicals or inorganic complexes possessing a transition metal ion. The basic physical concepts of EPR are analogous to those of nuclear magnetic resonance (NMR), but it is electron spins that are excited instead of spins of atomic nuclei. Because most stable molecules have all their electrons paired, the EPR technique is less widely used than NMR. However, this limitation to paramagnetic species also means that the EPR technique is one of great specificity, since ordinary chemical solvents and matrices do not give rise to EPR spectra.

EPR was first observed in Kazan State University by Soviet physicist Yevgeny Zavoisky in 1944, and was developed independently at the same time by Brebis Bleaney at Oxford University.

Theory

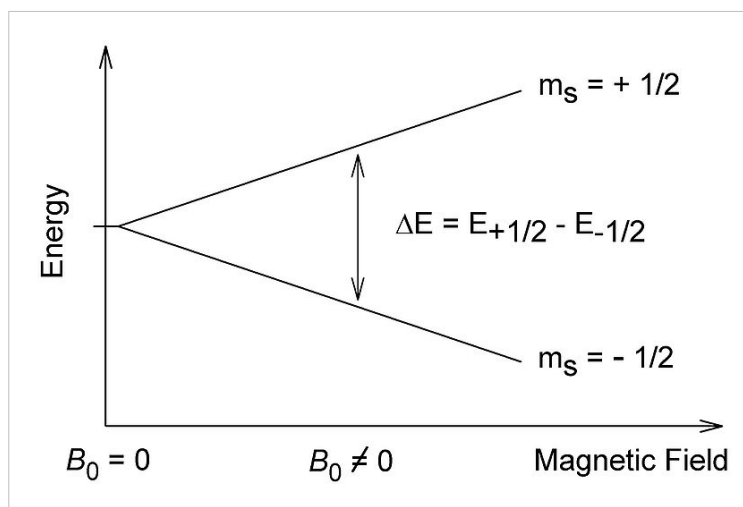
Origin of an EPR signal

Every electron has a magnetic moment and spin quantum number $s = 1/2$, with magnetic components $m_s = +1/2$ and $m_s = -1/2$. In the presence of an external magnetic field with strength B_0 , the electron's magnetic moment aligns itself either parallel ($m_s = -1/2$) or antiparallel ($m_s = +1/2$) to the field, each alignment having a specific energy (see the Zeeman effect). The parallel alignment corresponds to the lower energy state, and



EPR spectrometer

the separation between it and the upper state is $\Delta E = g_e \mu_B B_0$, where g_e is the electron's so-called g -factor (see also the Landé g -factor) and μ_B is the Bohr magneton. This equation implies that the splitting of the energy levels is directly proportional to the magnetic field's strength, as shown in the diagram below.

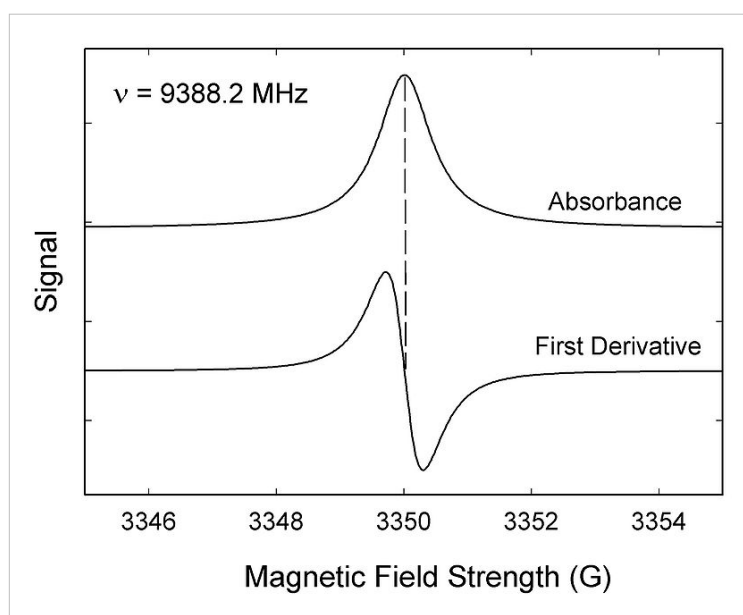


An unpaired electron can move between the two energy levels by either absorbing or emitting electromagnetic radiation of energy $\epsilon = h \nu$ such that the resonance condition, $\epsilon = \Delta E$, is obeyed. Substituting in $\epsilon = h \nu$ and $\Delta E = g_e \mu_B B_0$ leads to the fundamental equation of EPR spectroscopy: $h \nu = g_e \mu_B B_0$. Experimentally, this equation permits a large combination of frequency and magnetic field values, but the great majority of EPR measurements are made with microwaves in the 9000 – 10000 MHz (9 – 10 GHz) region, with fields corresponding to about 3500 G (0.35 T). See below for other field-frequency combinations.

In principle, EPR spectra can be generated by either varying the photon frequency incident on a sample while holding the magnetic field constant, or doing the reverse. In practice, it is usually the frequency which is kept fixed. A collection of paramagnetic centers, such as free radicals, is exposed to microwaves at a fixed frequency. By increasing an external magnetic field, the gap between the $m_s = +1/2$ and $m_s = -1/2$ energy states is widened until it matches the energy of the microwaves, as represented by the double-arrow in the diagram above. At this point the unpaired electrons can move between their two spin states. Since there typically are more electrons in the lower state, due to the Maxwell-Boltzmann distribution (see below), there is a net absorption of energy, and it is this absorption which is monitored and converted into a spectrum.

As an example of how $h\nu = g_e \mu_B B_0$ can be used, consider the case of a free electron, which has $g_e = 2.0023$,^[1] and the simulated spectrum shown at the right in two different forms. For the microwave frequency of 9388.2 MHz, the predicted resonance position is a magnetic field of about $B_0 = h \nu / g_e \mu_B = 0.3350$ tesla = 3350 gauss, as shown. Note that while two forms of the same spectrum are presented in the figure, most EPR spectra are recorded and published only as first derivatives.

Because of electron-nuclear mass differences, the magnetic moment of an



electron is substantially larger than the corresponding quantity for any nucleus, so that a much higher electromagnetic frequency is needed to bring about a spin resonance with an electron than with a nucleus, at identical magnetic field strengths. For example, for the field of 3350 G shown at the right, spin resonance occurs near 9388.2 MHz for an electron compared to only about 14.3 MHz for ^1H nuclei. (For NMR spectroscopy, the corresponding resonance equation is $h\nu = g_N \mu_N B_0$ where g_N and μ_N depend on the nucleus under study.)

Maxwell-Boltzmann distribution

In practice, EPR samples consist of collections of many paramagnetic species, and not single isolated paramagnetic centers. If the population of radicals is in thermodynamic equilibrium, its statistical distribution is described by the Maxwell-Boltzmann equation

$$\frac{n_{\text{upper}}}{n_{\text{lower}}} = \exp\left(-\frac{E_{\text{upper}} - E_{\text{lower}}}{kT}\right) = \exp\left(-\frac{\Delta E}{kT}\right) = \exp\left(-\frac{\epsilon}{kT}\right) = \exp\left(-\frac{h\nu}{kT}\right)$$

where n_{upper} is the number of paramagnetic centers occupying the upper energy state, k is the Boltzmann constant, and T is the temperature in kelvins. At 298 K, X-band microwave frequencies ($\nu \approx 9.75$ GHz) give $n_{\text{upper}}/n_{\text{lower}} \approx 0.998$, meaning that the upper energy level has a smaller population than the lower one. Therefore, transitions from the lower to the higher level are more probable than the reverse, which is why there is a net absorption of energy.

The sensitivity of the EPR method (i.e., the minimum number of detectable spins N_{min}) depends on the photon frequency ν according to

$$N_{\text{min}} = \frac{k_1 V}{Q_0 k_f \nu^2 P^{1/2}}$$

where k_1 is a constant, V is the sample's volume, Q_0 is the unloaded quality factor of the microwave cavity (sample chamber), k_f is the cavity filling coefficient, and P is the microwave power in the spectrometer cavity. With k_f and P being constants, $N_{\text{min}} \sim (Q_0 \nu^2)^{-1}$, i.e., $N_{\text{min}} \sim \nu^{-\alpha}$, where $\alpha \approx 1.5$. In practice, α can change varying from 0.5 to 4.5 depending on spectrometer characteristics, resonance conditions, and sample size. In other words, the higher the spectrometer frequency the lower the detection limit (N_{min}), meaning greater sensitivity.

Spectral parameters

In real systems, electrons are normally not solitary, but are associated with one or more atoms. There are several important consequences of this:

1. An unpaired electron can gain or lose angular momentum, which can change the value of its g -factor, causing it to differ from g_e . This is especially significant for chemical systems with transition-metal ions.
2. If an atom with which an unpaired electron is associated has a non-zero nuclear spin, then its magnetic moment will affect the electron. This leads to the phenomenon of hyperfine coupling, analogous to J-coupling in NMR, splitting the EPR resonance signal into doublets, triplets and so forth.
3. Interactions of an unpaired electron with its environment influence the shape of an EPR spectral line. Line shapes can yield information about, for example, rates of chemical reactions.
4. The g -factor and hyperfine coupling in an atom or molecule may not be the same for all orientations of an unpaired electron in an external magnetic field. This anisotropy depends upon the electronic structure of the atom or molecule (e.g., free radical) in question, and so can provide information about the atomic or molecular orbital containing the unpaired electron.

The g factor

Knowledge of the g -factor can give information about a paramagnetic center's electronic structure. An unpaired electron responds not only to a spectrometer's applied magnetic field B_0 , but also to any local magnetic fields of atoms or molecules. The effective field B_{eff} experienced by an electron is thus written

$$B_{\text{eff}} = B_0(1 - \sigma)$$

where σ includes the effects of local fields (σ can be positive or negative). Therefore, the $h\nu = g\mu_B B_{\text{eff}}$ resonance condition (above) is rewritten as follows:

$$h\nu = g\mu_B B_{\text{eff}} = g\mu_B B_0(1 - \sigma)$$

The quantity $g_e(1 - \sigma)$ is denoted g and called simply the g -factor, so that the final resonance equation becomes

$$h\nu = g\mu_B B_0$$

This last equation is used to determine g in an EPR experiment by measuring the field and the frequency at which resonance occurs. If g does not equal g_e the implication is that the ratio of the unpaired electron's spin magnetic moment to its angular momentum differs from the free electron value. Since an electron's spin magnetic moment is constant (approximately the Bohr magneton), then the electron must have gained or lost angular momentum through spin-orbit coupling. Because the mechanisms of spin-orbit coupling are well understood, the magnitude of the change gives information about the nature of the atomic or molecular orbital containing the unpaired electron.

Hyperfine coupling

Since the source of an EPR spectrum is a change in an electron's spin state, it might be thought that all EPR spectra would consist of a single line. However, the interaction of an unpaired electron, by way of its magnetic moment, with nearby nuclear spins, results in additional allowed energy states and, in turn, multi-lined spectra. In such cases, the spacing between the EPR spectral lines indicates the degree of interaction between the unpaired electron and the perturbing nuclei. The hyperfine coupling constant of a nucleus is directly related to the spectral line spacing and, in the simplest cases, is essentially the spacing itself.

Two common mechanisms by which electrons and nuclei interact are the Fermi contact interaction and by dipolar interaction. The former applies largely to the case of isotropic interactions (independent of sample orientation in a magnetic field) and the latter to the case of anisotropic interactions (spectra dependent on sample orientation in a magnetic field). Spin polarization is a third mechanism for interactions between an unpaired electron and a nuclear spin, being especially important for π -electron organic radicals, such as the benzene radical anion. The symbols " a " or " A " are used for isotropic hyperfine coupling constants while " B " is usually employed for anisotropic hyperfine coupling constants.^[2]

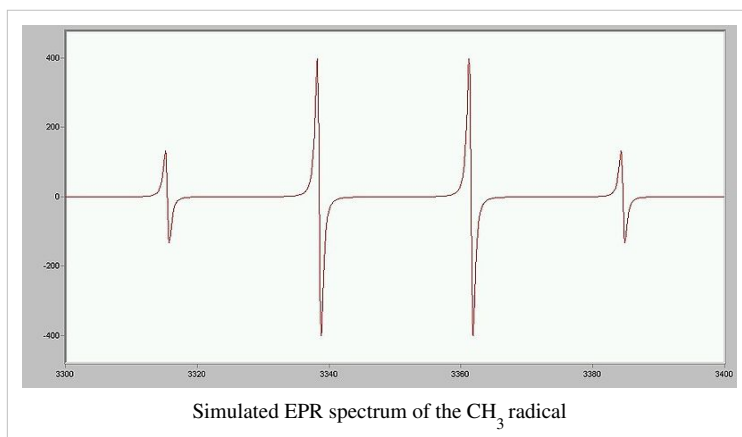
In many cases, the isotropic hyperfine splitting pattern for a radical freely tumbling in a solution (isotropic system) can be predicted.

- For a radical having M equivalent nuclei, each with a spin of I , the number of EPR lines expected is $2MI + 1$. As an example, the methyl radical, CH_3 , has three ^1H nuclei each with $I = 1/2$, and so the number of lines expected is $2MI + 1 = 2(3)(1/2) + 1 = 4$, which is as observed.
- For a radical having M_1 equivalent nuclei, each with a spin of I_1 , and a group of M_2 equivalent nuclei, each with a spin of I_2 , the number of lines expected is $(2M_1I_1 + 1)(2M_2I_2 + 1)$. As an example, the methoxymethyl radical, $\text{H}_2\text{C}(\text{OCH}_3)$, has two equivalent ^1H nuclei each with $I = 1/2$ and three equivalent ^1H nuclei each with $I = 1/2$, and so the number of lines expected is $(2M_1I_1 + 1)(2M_2I_2 + 1) = [2(2)(1/2) + 1][2(3)(1/2) + 1] = [3][4] = 12$, again as observed.

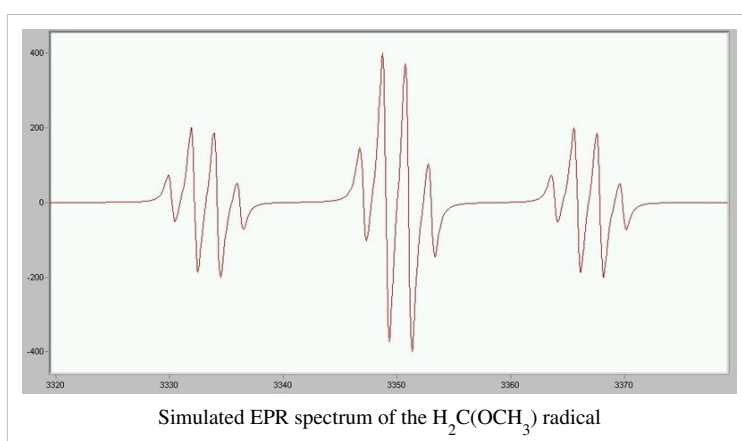
- The above can be extended to predict the number of lines for any number of nuclei.

While it is easy to predict the number of lines a radical's EPR spectrum should show, the reverse problem, unraveling a complex multi-line EPR spectrum and assigning the various spacings to specific nuclei, is more difficult.

In the oft-encountered case of $I = 1/2$ nuclei (e.g., ^1H , ^{19}F , ^{31}P), the line intensities produced by a population of radicals, each possessing M equivalent nuclei, will follow Pascal's triangle. For example, the spectrum at the right shows that the three ^1H nuclei of the CH_3 radical give rise to $2MI + 1 = 2(3)(1/2) + 1 = 4$ lines with a 1:3:3:1 ratio. The line spacing gives a hyperfine coupling constant of $a_{\text{H}} = 23 \text{ G}$ for each of the three ^1H nuclei. Note again that the lines in this spectrum are *first derivatives* of absorptions.



As a second example, consider the methoxymethyl radical, $\text{H}_2\text{C}(\text{OCH}_3)$. The two equivalent methyl hydrogens will give an overall 1:2:1 EPR pattern, each component of which is further split by the three methoxy hydrogens into a 1:3:3:1 pattern to give a total of $3 \times 4 = 12$ lines, a triplet of quartets. A simulation of the observed EPR spectrum is shown at the right, and agrees with the 12-line prediction and the expected line intensities. Note that the smaller coupling constant (smaller line spacing) is due to the three methoxy hydrogens, while the larger coupling constant (line spacing) is from the two hydrogens bonded directly to the carbon atom bearing the unpaired electron. It is often the case that coupling constants decrease in size with distance from a radical's unpaired electron, but there are some notable exceptions, such as the ethyl radical (CH_2CH_3).



Resonance linewidth definition

Resonance linewidths are defined in terms of the magnetic induction B , and its corresponding units, and are measured along the x axis of an EPR spectrum, from a line's center to a chosen reference point of the line. These defined widths are called halfwidths and possess some advantages: for asymmetric lines values of left and right halfwidth can be given. The halfwidth ΔB_h is the distance measured from the line's center to the point in which absorption value has half of maximal absorption value in the center of resonance line. First inclination width $\Delta B_{1/2}$ is a distance from center of the line to the point of maximal absorption curve inclination. In practice, a full definition of linewidth is used. For symmetric lines, halfwidth $\Delta B_{1/2} = 2\Delta B_h$, and full inclination width $\Delta B_{max} = 2\Delta B_{1s}$.

Applications

EPR spectroscopy is used in various branches of science, such as chemistry and physics, for the detection and identification of free radicals and paramagnetic centers such as F centers. EPR is a sensitive, specific method for studying both radicals formed in chemical reactions and the reactions themselves. For example, when frozen water (solid H_2O) is decomposed by exposure to high-energy radiation, radicals such as H, OH, and HO_2 are produced. Such radicals can be identified and studied by EPR. Organic and inorganic radicals can be detected in electrochemical systems and in materials exposed to UV light. In many cases, the reactions to make the radicals and the subsequent reactions of the radicals are of interest, while in other cases EPR is used to provide information on a radical's geometry and the orbital of the unpaired electron.

Medical and biological applications of EPR also exist. Although radicals are very reactive, and so do not normally occur in high concentrations in biology, special reagents have been developed to spin-label molecules of interest. These reagents are particularly useful in biological systems. Specially-designed nonreactive radical molecules can attach to specific sites in a biological cell, and EPR spectra can then give information on the environment of these so-called spin-label or spin-probes.

A type of dosimetry system has been designed for reference standards and routine use in medicine, based on EPR signals of radicals from irradiated polycrystalline α -alanine (the alanine deamination radical, the hydrogen abstraction radical, and the $(\text{CO}^-(\text{OH}))=\text{C}(\text{CH}_3)\text{NH}_2^+$ radical). This method is suitable for measuring gamma and x-rays, electrons, protons, and high-linear energy transfer (LET) radiation of doses in the 1 Gy to 100 kGy range.^[3]

EPR spectroscopy can only be applied to systems in which the balance between radical decay and radical formation keeps the free-radicals concentration above the detection limit of the spectrometer used. This can be a particularly severe problem in studying reactions in liquids. An alternative approach is to slow down reactions by studying samples held at cryogenic temperatures, such as 77 K (liquid nitrogen) or 4.2 K (liquid helium). An example of this work is the study of radical reactions in single crystals of amino acids exposed to x-rays, work that sometimes leads to activation energies and rate constants for radical reactions.

The study of radiation-induced free radicals in biological substances (for cancer research) poses the additional problem that tissue contains water, and water (due to its electric dipole moment) has a strong absorption band in the microwave region used in EPR spectrometers.

EPR also has been used by archaeologists for the dating of teeth. Radiation damage over long periods of time creates free radicals in tooth enamel, which can then be examined by EPR and, after proper calibration, dated. Alternatively, material extracted from the teeth of people during dental procedures can be used to quantify their cumulative exposure to ionizing radiation. People exposed to radiation from the Chernobyl disaster have been examined by this method.^{[4] [5]}

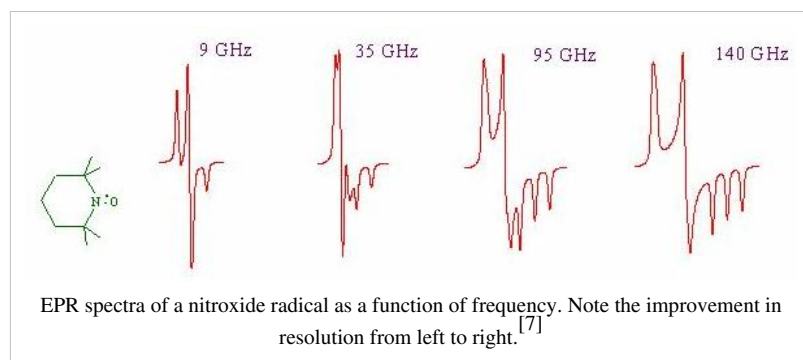
Radiation-sterilized foods have been examined with EPR spectroscopy, the aim being to develop methods to determine if a particular food sample has been irradiated and to what dose.

Because of its high sensitivity, EPR was used recently to measure the quantity of energy used locally during a mechanochemical milling process.^[6]

High-field high-frequency measurements

High-field-high-frequency EPR measurements are sometimes needed to detect subtle spectroscopic details. However, for many years the use of electromagnets to produce the needed fields above 1.5 T was impossible, due principally to limitations of traditional magnet materials. The first multifunctional millimeter EPR spectrometer with a superconducting solenoid was described in the early 1970s by Prof. Y. S. Lebedev's group (Russian Institute of Chemical Physics, Moscow) in collaboration with L. G. Oranski's group (Ukrainian Physics and Technics Institute, Donetsk) which began working in the Institute of Problems of Chemical Physics, Chernogolovka around 1975.^[7] Two decades later, a W-band EPR spectrometer was produced as a small commercial line by the German Bruker

Company, initiating the expansion of W-band EPR techniques into medium-sized academic laboratories. Today there still are only a few scientific centers in the world capable of high-field-high-frequency EPR, among them are the Grenoble High Magnetic Field Laboratory in Grenoble, France, the Physics Department in Freie Universität Berlin, the National High Magnetic Field Laboratory in Tallahassee, US, the National Center for Advanced ESR Technology (ACERT) at Cornell University in Ithaca, US, the Department of Physiology and Biophysics at Albert Einstein College of Medicine, Bronx, NY, the IFW in Dresden, Germany, the Institute of Physics of Complex Matter in Lausanne in Switzerland, and the Institute of Physics of the Leiden University, Netherlands.



Waveband	L	S	C	X	P	K	Q	U	V	E	W	F	D	—	J	—
λ/mm	300	100	75	30	20	12.5	8.5	6	4.6	4	3.2	2.7	2.1	1.6	1.1	0.83
ν/GHz	1	3	4	10	15	24	35	50	65	75	95	111	140	190	285	360
B_0/T	0.03	0.11	0.14	0.33	0.54	0.86	1.25	1.8	2.3	2.7	3.5	3.9	4.9	6.8	10.2	12.8

The EPR waveband is stipulated by the frequency or wavelength of a spectrometer's microwave source (see Table).

EPR experiments often are conducted at X and, less commonly, Q bands, mainly due to the ready availability of the necessary microwave components (which originally were developed for radar applications). A second reason for widespread X and Q band measurements is that electromagnets can reliably generate fields up to about 1 tesla. However, the low spectral resolution over g -factor at these wavebands limits the study of paramagnetic centers with comparatively low anisotropic magnetic parameters. Measurements at $\nu > 40$ GHz, in the millimeter wavelength region, offer the following advantages:

1. EPR spectra are simplified due to the reduction of second-order effects at high fields.
2. Increase in orientation selectivity and sensitivity in the investigation of disordered systems.
3. The informativity and precision of pulse methods, e.g., ENDOR also increase at high magnetic fields.
4. Accessibility of spin systems with larger zero-field splitting due to the larger microwave quantum energy $h\nu$.
5. The higher spectral resolution over g -factor, which increases with irradiation frequency ν and external magnetic field B_0 . This is used to investigate the structure, polarity, and dynamics of radical microenvironments in spin-modified organic and biological systems through the spin label and probe method. The figure shows how spectral resolution improves with increasing frequency.
6. Saturation of paramagnetic centers occurs at a comparatively low microwave polarizing field B_1 , due to the exponential dependence of the number of excited spins on the radiation frequency ν . This effect can be successfully used to study the relaxation and dynamics of paramagnetic centers as well as of superslow motion in the systems under study.
7. The cross-relaxation of paramagnetic centers decreases dramatically at high magnetic fields, making it easier to obtain more-precise and more-complete information about the system under study.^[7]

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Further reading

Many good books and papers are available on the subject of EPR spectroscopy, including those listed here. Essentially all details in this article can be found in these.

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External links

- Electron Magnetic Resonance Program (<http://www.magnet.fsu.edu/usershub/scientificdivisions/emr/overview.html>) National High Magnetic Field Laboratory

Fluorescence spectroscopy

Fluorescence spectroscopy aka fluorometry or spectrofluorometry, is a type of electromagnetic spectroscopy which analyzes fluorescence from a sample. It involves using a beam of light, usually ultraviolet light, that excites the electrons in molecules of certain compounds and causes them to emit light of a lower energy, typically, but not necessarily, visible light. A complementary technique is absorption spectroscopy.

Devices that measure fluorescence are called fluorometers or fluorimeters.

Theory

Molecules have various states referred to as energy levels. Fluorescence spectroscopy is primarily concerned with electronic and vibrational states. Generally, the species being examined has a ground electronic state (a low energy state) of interest, and an excited electronic state of higher energy. Within each of these electronic states are various vibrational states.

In fluorescence spectroscopy, the species is first excited, by absorbing a photon, from its ground electronic state to one of the various vibrational states in the excited electronic state. Collisions with other molecules cause the excited molecule to lose vibrational energy until it reaches the lowest vibrational state of the excited electronic state.

The molecule then drops down to one of the various vibrational levels of the ground electronic state again, emitting a photon in the process. As molecules may drop down into any of several vibrational levels in the ground state, the emitted photons will have different energies, and thus frequencies. Therefore, by analysing the different frequencies of light emitted in fluorescent spectroscopy, along with their relative intensities, the structure of the different vibrational levels can be determined.

In a typical experiment, the different wavelengths of fluorescent light emitted by a sample are measured using a monochromator, holding the excitation light at a constant wavelength. This is called an *emission spectrum*. An *excitation spectrum* is the opposite, whereby the emission light is held at a constant wavelength, and the excitation light is scanned through many different wavelengths (via a monochromator). An *Emission Map* is measured by recording a number of different emission spectra created from different excitation wavelengths, and combining them all together. This is a three dimensional data set, intensity of emission as a function of excitation and emission wavelengths, and is typically depicted as a contour map.

Instrumentation

Two general types of instruments exist:

- Filter fluorometers use filters to isolate the incident light and fluorescent light.
- Spectrofluorometers use diffraction grating monochromators to isolate the incident light and fluorescent light.

Both types use the following scheme: The light from an excitation source passes through a filter or monochromator, and strikes the sample. A proportion of the incident light is absorbed by the sample, and some of the molecules in the sample fluoresce. The fluorescent light is emitted in all directions. Some of this fluorescent light passes through a second filter or monochromator and reaches a detector, which is usually placed at 90° to the incident light beam to minimize the risk of transmitted or reflected incident light reaching the detector.

Various light sources may be used as excitation sources, including lasers, photodiodes, and lamps; xenon arcs and mercury-vapor lamps in particular. A laser only emits light of high irradiance at a very narrow wavelength interval, typically under 0.01 nm, which makes an excitation monochromator or filter unnecessary. The disadvantage of this method is that the wavelength of a laser cannot be changed by much. A mercury vapor lamp is a line lamp, meaning it emits light near peak wavelengths. By contrast, a xenon arc has a continuous emission spectrum with nearly constant intensity in the range from 300-800 nm and a sufficient irradiance for measurements down to just above 200 nm.

Filters and/or monochromators may be used in fluorimeters. A monochromator transmits light of an adjustable wavelength with an adjustable tolerance. The most common type of monochromator utilizes a diffraction grating, that is, collimated light illuminates a grating and exits with a different angle depending on the wavelength. The monochromator can then be adjusted to select which wavelengths to transmit. For allowing anisotropy measurements the addition of two polarization filters are necessary: One after the excitation monochromator or filter, and one before the emission monochromator or filter.

As mentioned before, the fluorescence is most often measured at a 90° angle relative to the excitation light. This geometry is used instead of placing the sensor at the line of the excitation light at a 180° angle in order to avoid interference of the transmitted excitation light. No monochromator is perfect and it will transmit some stray light, that is, light with other wavelengths than the targeted. An ideal monochromator would only transmit light in the specified range and have a high wavelength-independent transmission. When measuring at a 90 angle, only the light scattered by the sample causes stray light. This results in a better signal-to-noise ratio, and lowers the detection limit by approximately a factor 10000 ^[1], when compared to the 180° geometry. Furthermore, the fluorescence can also be measured from the front, which is often done for turbid or opaque samples ^[2].

The detector can either be single-channeled or multichanneled. The single-channeled detector can only detect the intensity of one wavelength at a time, while the multichanneled detects the intensity at all wavelengths simultaneously, making the emission monochromator or filter unnecessary. The different types of detectors have both advantages and disadvantages.

The most versatile fluorimeters with dual monochromators and a continuous excitation light source can record both an excitation spectrum and a fluorescence spectrum. When measuring fluorescence spectra, the wavelength of the excitation light is kept constant, preferably at a wavelength of high absorption, and the emission monochromator scans the spectrum. For measuring excitation spectra, the wavelength passing through the emission filter or monochromator is kept constant and the excitation monochromator is scanning. The excitation spectrum generally is identical to the absorption spectrum as the fluorescence intensity is proportional to the absorption. ^[3]

Analysis of data

At low concentrations the fluorescence intensity will generally be proportional to the concentration of the fluorophore.

Unlike in UV/visible spectroscopy, 'standard', device independent spectra are not easily attained. Several factors influence and distort the spectra, and corrections are necessary to attain 'true', i.e. machine-independent, spectra. The different types of distortions will here be classified as being either instrument- or sample-related. Firstly, the distortion arising from the instrument is discussed. As a start, the light source intensity and wavelength characteristics varies over time during each experiment and between each experiment. Furthermore, no lamp has a constant intensity at all wavelengths. To correct this, a beam splitter can be applied after the excitation monochromator or filter to direct a portion of the light to a reference detector.

Additionally, the transmission efficiency of monochromators and filters must be taken into account. These may also change over time. The transmission efficiency of the monochromator also varies depending on wavelength. This is the reason that an optional reference detector should be placed after the excitation monochromator or filter. The percentage of the fluorescence picked up by the detector is also dependent upon the system. Furthermore, the

detector quantum efficiency, that is, the percentage of photons detected, varies between different detectors, with wavelength and with time, as the detector inevitably deteriorates.

Two other topics that must be considered include the optics used to direct the radiation and the means of holding or containing the sample material (called a cuvette or cell). For most UV, visible, and NIR measurements the use of precision quartz cuvettes is necessary. In both cases, it is important to select materials that have relatively little absorption in the wavelength range of interest. Quartz is ideal because it transmits from 200nm-2500nm; higher grade quartz can even transmit up to 3500nm, whereas the absorption properties of other materials can mask the fluorescence from the sample.

Correction of all these instrumental factors for getting a 'standard' spectrum is a tedious process, which is only applied in practice when it is strictly necessary. This is the case when measuring the quantum yield or when finding the wavelength with the highest emission intensity for instance.

As mentioned earlier, distortions arise from the sample as well. Therefore some aspects of the sample must be taken into account too. Firstly, photodecomposition may decrease the intensity of fluorescence over time. Scattering of light must also be taken into account. The most significant types of scattering in this context are Rayleigh and Raman scattering. Light scattered by Rayleigh scattering has the same wavelength as the incident light, whereas in Raman scattering the scattered light changes wavelength usually to longer wavelengths. Raman scattering is the result of a virtual electronic state induced by the excitation light. From this virtual state, the molecules may relax back to a vibrational level other than the vibrational ground state ^[4]. In fluorescence spectra, it is always seen at a constant wavenumber difference relative to the excitation wavenumber e.g. the peak appears at a wavenumber 3600 cm⁻¹ lower than the excitation light in water.

Other aspects to consider are the inner filter effects. These include reabsorption. Reabsorption happens because another molecule or part of a macromolecule absorbs at the wavelengths at which the fluorophore emits radiation. If this is the case, some or all of the photons emitted by the fluorophore may be absorbed again. Another inner filter effect occurs because of high concentrations of absorbing molecules, including the fluorophore. The result is that the intensity of the excitation light is not constant throughout the solution. Resultingly, only a small percentage of the excitation light reaches the fluorophores that are visible for the detection system. The inner filter effects change the spectrum and intensity of the emitted light and they must therefore be considered when analysing the emission spectrum of fluorescent light. ^[5] ^[6]

Tryptophan Fluorescence

The fluorescence of a folded protein is a mixture of the fluorescence from individual aromatic residues. Most of the intrinsic fluorescence emissions of a folded protein are due to excitation of tryptophan residues, with some emissions due to tyrosine and phenylalanine; but disulfide bonds also have appreciable absorption in this wavelength range. Typically, tryptophan has a wavelength of maximum absorption of 280 nm and an emission peak that is solvatochromic, ranging from ca. 300 to 350 nm depending in the polarity of the local environment ^[7] Hence, protein fluorescence may be used as a diagnostic of the conformational state of a protein. ^[8] Furthermore, tryptophan fluorescence is strongly influenced by the proximity of other residues (*i.e.*, nearby *protonated* groups such as Asp or Glu can cause quenching of Trp fluorescence). Also, energy transfer between tryptophan and the other fluorescent amino acids is possible, which would affect the analysis, especially in cases where the Förster acidic approach is taken. In addition, tryptophan is a relatively rare amino acid; many proteins contain only one or a few tryptophan residues. Therefore, tryptophan fluorescence can be a very sensitive measurement of the conformational state of individual tryptophan residues. The advantage compared to extrinsic probes is that the protein itself is not changed. The use of intrinsic fluorescence for the study of protein conformation is in practice limited to cases with few (or perhaps only one) tryptophan residues, since each experiences a different local environment, which gives rise to different emission spectra.

Tryptophan is an important intrinsic fluorescent probe (amino acid), which can be used to estimate the nature of microenvironment of the tryptophan. When performing experiments with denaturants, surfactants or other amphiphilic molecules, the microenvironment of the tryptophan might change. For example, if a protein containing a single tryptophan in its 'hydrophobic' core is denatured with increasing temperature, a red-shift emission spectrum will appear. This is due to the exposure of the tryptophan to an aqueous environment as opposed to a hydrophobic protein interior. In contrast, the addition of a surfactant to a protein which contains a tryptophan which is exposed to the aqueous solvent will cause a blue shifted emission spectrum if the tryptophan is embedded in the surfactant vesicle or micelle^[9]. Proteins that lack tryptophan may be coupled to a fluorophore.

At 295 nm, the tryptophan emission spectrum is dominant over the weaker tyrosine and phenylalanine fluorescence.

Applications

Fluorescence spectroscopy is used in, among others, biochemical, medical, and chemical research fields for analyzing organic compounds. There has also been a report of its use in differentiating malignant, bashful skin tumors from benign.

Atomic Fluorescence Spectroscopy (AFS) techniques are useful in other kinds of analysis/measurement of a compound present in air or water, or other media, such as CVAFS which is used for heavy metals detection, such as mercury.

Fluorescence can also be used to redirect photons, see fluorescent solar collector.

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External links

- Time resolved fluorescence spectroscopy (http://content.piaction.com/Uploads/Princeton/Documents/Library/UpdatedLibrary/Time_resolved_fluorescence_spectroscopy.pdf), princetoninstruments.com

Fluorescence correlation spectroscopy

Fluorescence correlation spectroscopy (FCS) is a correlation analysis of fluctuation of the fluorescence intensity. The analysis provides parameters of the physics under the fluctuations. One of the interesting applications of this is an analysis of the concentration fluctuations of fluorescent particles (molecules) in solution. In this application, the fluorescence emitted from a very tiny space in solution containing a small number of fluorescent particles (molecules) is observed. The fluorescence intensity is fluctuating due to Brownian motion of the particles. In other words, the number of the particles in the sub-space defined by the optical system is randomly changing around the average number. The analysis gives the average number of fluorescent particles and average diffusion time, when the particle is passing through the space. Eventually, both the concentration and size of the particle (molecule) are determined. Since the method is observing a small number of molecule in a very tiny spot, it is a very sensitive analytical tool. Both parameters are important in biochemical research, biophysics, and chemistry. In contrast to other methods, such as HPLC analysis, FCS has no physical separation process and has a good spatial resolution determined by the optics. These are of great advantage. Moreover, the method enables us to observe fluorescence-tagged molecules in the biochemical pathway in intact living cells. This opens a new area, "in situ or in vivo biochemistry": tracing the biochemical pathway in intact cells and organs.

Commonly, FCS is employed in the context of optical microscopy, in particular confocal or two-photon microscopy. In these techniques light is focused on a sample and the measured fluorescence intensity fluctuations (due to diffusion, physical or chemical reactions, aggregation, etc.) are analyzed using the temporal autocorrelation. Because the measured property is essentially related to the magnitude and/or the amount of fluctuations, there is an optimum measurement regime at the level when individual species enter or exit the observation volume (or turn on and off in the volume). When too many entities are measured at the same time the overall fluctuations are small in comparison to the total signal and may not be resolvable – in the other direction, if the individual fluctuation-events are too sparse in time, one measurement may take prohibitively too long. FCS is in a way the fluorescent counterpart to dynamic light scattering, which uses coherent light scattering, instead of (incoherent) fluorescence.

When an appropriate model is known, FCS can be used to obtain quantitative information such as

- diffusion coefficients
- hydrodynamic radii
- average concentrations
- kinetic chemical reaction rates
- singlet-triplet dynamics

Because fluorescent markers come in a variety of colors and can be specifically bound to a particular molecule (e.g. proteins, polymers, metal-complexes, etc.), it is possible to study the behavior of individual molecules (in rapid succession in composite solutions). With the development of sensitive detectors such as avalanche photodiodes the detection of the fluorescence signal coming from individual molecules in highly dilute samples has become practical. With this emerged the possibility to conduct FCS experiments in a wide variety of specimens, ranging from materials science to biology. The advent of engineered cells with genetically tagged proteins (like green fluorescent protein) has made FCS a common tool for studying molecular dynamics in living cells.

History

Signal-correlation techniques were first experimentally applied to fluorescence in 1972 by Magde, Elson, and Webb^[1], who are therefore commonly credited as the "inventors" of FCS. The technique was further developed in a group of papers by these and other authors soon after, establishing the theoretical foundations and types of applications.^{[2] [3] [4]} See Thompson (1991)^[5] for a review of that period.

Beginning in 1993^[6], a number of improvements in the measurement techniques—notably using confocal microscopy, and then two-photon microscopy—to better define the measurement volume and reject background—greatly improved the signal-to-noise ratio and allowed single molecule sensitivity.^{[7] [8]} Since then, there has been a renewed interest in FCS, and as of August 2007 there have been over 3,000 papers using FCS found in Web of Science. See Krichevsky and Bonnet^[9] for a recent review. In addition, there has been a flurry of activity extending FCS in various ways, for instance to laser scanning and spinning-disk confocal microscopy (from a stationary, single point measurement), in using cross-correlation (FCCS) between two fluorescent channels instead of autocorrelation, and in using Förster Resonance Energy Transfer (FRET) instead of fluorescence.

Typical FCS setup

The typical FCS setup consists of a laser line (wavelengths ranging typically from 405–633 nm (cw), and from 690–1100 nm (pulsed)), which is reflected into a microscope objective by a dichroic mirror. The laser beam is focused in the sample, which contains fluorescent particles (molecules) in such high dilution, that only a few are within the focal spot (usually 1–100 molecules in one fL). When the particles cross the focal volume, they fluoresce. This light is collected by the same objective and, because it is red-shifted with respect to the excitation light it passes the dichroic mirror reaching a detector, typically a photomultiplier tube or avalanche photodiode detector. The resulting electronic signal can be stored either directly as an intensity versus time trace to be analyzed at a later point, or computed to generate the autocorrelation directly (which requires special acquisition cards). The FCS curve by itself only represents a time-spectrum. Conclusions on physical phenomena have to be extracted from there with appropriate models. The parameters of interest are found after fitting the autocorrelation curve to modeled functional forms.^[10]

The measurement volume

The measurement volume is a convolution of illumination (excitation) and detection geometries, which result from the optical elements involved. The resulting volume is described mathematically by the point spread function (or PSF), it is essentially the image of a point source. The PSF is often described as an ellipsoid (with unsharp boundaries) of few hundred nanometers in focus diameter, and almost one micrometre along the optical axis. The shape varies significantly (and has a large impact on the resulting FCS curves) depending on the quality of the optical elements (it is crucial to avoid astigmatism and to check the real shape of the PSF on the instrument). In the case of confocal microscopy, and for small pinholes (around one Airy unit), the PSF is well approximated by Gaussians:

$$PSF(r, z) = I_0 e^{-2r^2/\omega_{xy}^2} e^{-2z^2/\omega_z^2}$$

where I_0 is the peak intensity, r and z are radial and axial position, and ω_{xy} and ω_z are the radial and axial radii, and $\omega_z > \omega_{xy}$. This Gaussian form is assumed in deriving the functional form of the autocorrelation.

Typically ω_{xy} is 200–300 nm, and ω_z is 2–6 times larger.^[11] One common way of calibrating the measurement volume parameters is to perform FCS on a species with known diffusion coefficient and concentration (see below). Diffusion coefficients for common fluorophores in water are given in a later section.

The Gaussian approximation works to varying degrees depending on the optical details, and corrections can sometimes be applied to offset the errors in approximation.^[12]

Autocorrelation function

The (temporal) autocorrelation function is the correlation of a time series with itself shifted by time τ , as a function of τ :

$$G(\tau) = \frac{\langle \delta I(t) \delta I(t + \tau) \rangle}{\langle I(t) \rangle^2} = \frac{\langle I(t) I(t + \tau) \rangle}{\langle I(t) \rangle^2} - 1$$

where $\delta I(t) = I(t) - \langle I(t) \rangle$ is the deviation from the mean intensity. The normalization (denominator) here is the most commonly used for FCS, because then the correlation at $\tau = 0$, $G(0)$, is related to the average number of particles in the measurement volume.

Interpreting the autocorrelation function

To extract quantities of interest, the autocorrelation data can be fitted, typically using a nonlinear least squares algorithm. The fit's functional form depends on the type of dynamics (and the optical geometry in question).

Normal diffusion

The fluorescent particles used in FCS are small and thus experience thermal motions in solution. The simplest FCS experiment is thus normal 3D diffusion, for which the autocorrelation is:

$$G(\tau) = G(0) \frac{1}{(1 + (\tau/\tau_D))(1 + a^{-2}(\tau/\tau_D))^{1/2}} + G(\infty)$$

where $a = \omega_z/\omega_{xy}$ is the ratio of axial to radial e^{-2} radii of the measurement volume, and τ_D is the characteristic residence time. This form was derived assuming a Gaussian measurement volume. Typically, the fit would have three free parameters— $G(0)$, $G(\infty)$, and τ_D —from which the diffusion coefficient and fluorophore concentration can be obtained.

With the normalization used in the previous section, $G(0)$ gives the mean number of diffusers in the volume $\langle N \rangle$, or equivalently—with knowledge of the observation volume size—the mean concentration:

$$G(0) = \frac{1}{\langle N \rangle} = \frac{1}{V_{\text{eff}} \langle C \rangle},$$

where the effective volume is found from integrating the Gaussian form of the measurement volume and is given by:

$$V_{\text{eff}} = \pi^{3/2} \omega_{xy}^2 \omega_z.$$

τ_D gives the diffusion coefficient:

$$D = \omega_{xy}^2 / 4\tau_D.$$

Anomalous diffusion

If the diffusing particles are hindered by obstacles or pushed by a force (molecular motors, flow, etc.) the dynamics is often not sufficiently well-described by the normal diffusion model, where the mean squared displacement (MSD) grows linearly with time. Instead the diffusion may be better described as anomalous diffusion, where the temporal dependence of the MSD is non-linear as in the power-law:

$$MSD = 6D_a t^\alpha$$

where D_a is an anomalous diffusion coefficient. "Anomalous diffusion" commonly refers only to this very generic model, and not the many other possibilities that might be described as anomalous. Also, a power law is, in a strict sense, the expected form only for a narrow range of rigorously defined systems, for instance when the distribution of obstacles is fractal. Nonetheless a power law can be a useful approximation for a wider range of systems.

The FCS autocorrelation function for anomalous diffusion is:

$$G(\tau) = G(0) \frac{1}{(1 + (\tau/\tau_D)^\alpha)(1 + a^{-2}(\tau/\tau_D)^\alpha)^{1/2}} + G(\infty),$$

where the anomalous exponent α is the same as above, and becomes a free parameter in the fitting.

Using FCS, the anomalous exponent has been shown to be an indication of the degree of molecular crowding (it is less than one and smaller for greater degrees of crowding)^[13].

Polydisperse diffusion

If there are diffusing particles with different sizes (diffusion coefficients), it is common to fit to a function that is the sum of single component forms:

$$G(\tau) = G(0) \sum_i \frac{\alpha_i}{(1 + (\tau/\tau_{D,i})) (1 + a^{-2}(\tau/\tau_{D,i}))^{1/2}} + G(\infty)$$

where the sum is over the number different sizes of particle, indexed by i , and α_i gives the weighting, which is related to the quantum yield and concentration of each type. This introduces new parameters, which makes the fitting more difficult as a higher dimensional space must be searched. Nonlinear least square fitting typically becomes unstable with even a small number of $\tau_{D,i}$ s. A more robust fitting scheme, especially useful for polydisperse samples, is the Maximum Entropy Method^[14].

Diffusion with flow

With diffusion together with a uniform flow with velocity v in the lateral direction, the autocorrelation is^[15]:

$$G(\tau) = G(0) \frac{1}{(1 + (\tau/\tau_D))(1 + a^{-2}(\tau/\tau_D))^{1/2}} \times \exp[-(\tau/\tau_v)^2 \times \frac{1}{1 + \tau/\tau_D}] + G(\infty)$$

where $\tau_v = \omega_{xy}/v$ is the average residence time if there is only a flow (no diffusion).

Chemical relaxation

A wide range of possible FCS experiments involve chemical reactions that continually fluctuate from equilibrium because of thermal motions (and then "relax"). In contrast to diffusion, which is also a relaxation process, the fluctuations cause changes between states of different energies. One very simple system showing chemical relaxation would be a stationary binding site in the measurement volume, where particles only produce signal when bound (e.g. by FRET, or if the diffusion time is much faster than the sampling interval). In this case the autocorrelation is:

$$G(\tau) = G(0) \exp(-\tau/\tau_B) + G(\infty)$$

where

$$\tau_B = (k_{on} + k_{off})^{-1}$$

is the relaxation time and depends on the reaction kinetics (on and off rates), and:

$$G(0) = \frac{1}{\langle N \rangle} \frac{k_{on}}{k_{off}} = \frac{1}{\langle N \rangle} K$$

is related to the equilibrium constant K .

Most systems with chemical relaxation also show measureable diffusion as well, and the autocorrelation function will depend on the details of the system. If the diffusion and chemical reaction are decoupled, the combined autocorrelation is the product of the chemical and diffusive autocorrelations.

Triplet state correction

The autocorrelations above assume that the fluctuations are not due to changes in the fluorescent properties of the particles. However, for the majority of (bio)organic fluorophores--e.g. green fluorescent protein, rhodamine, Cy3 and Alexa Fluor dyes--some fraction of illuminated particles are excited to a triplet state (or other non-radiative decaying states) and then do not emit photons for a characteristic relaxation time τ_F . Typically τ_F is on the order of microseconds, which is usually smaller than the dynamics of interest (e.g. τ_D) but large enough to be measured. A multiplicative term is added to the autocorrelation account for the triplet state. For normal diffusion:

$$G(\tau) = G(0) \frac{1 - F + Fe^{-\tau/\tau_F}}{1 - F} \frac{1}{(1 + (\tau/\tau_{D,i})) (1 + a^{-2}(\tau/\tau_{D,i}))^{1/2}} + G(\infty)$$

where F is the fraction of particles that have entered the triplet state and τ_F is the corresponding triplet state relaxation time. If the dynamics of interest are much slower than the triplet state relaxation, the short time component of the autocorrelation can simply be truncated and the triplet term is unnecessary.

Common fluorescent probes

The fluorescent species used in FCS is typically a biomolecule of interest that has been tagged with a fluorophore (using immunohistochemistry for instance), or is a naked fluorophore that is used to probe some environment of interest (e.g. the cytoskeleton of a cell). The following table gives diffusion coefficients of some common fluorophores in water at room temperature, and their excitation wavelengths.

Fluorescent dye	D ($\times 10^{-10} \text{ m}^2 \text{ s}^{-1}$)	Excitation wavelength (nm)	Reference
Rhodamine 6G	2.8, 3.0, 4.14 ± 0.05 @ 25.00 °C	514	[16] , [17] , [18]
Rhodamine 110	2.7	488	[19]
Tetramethyl rhodamine	2.6	543	
Cy3	2.8	543	
Cy5	$2.5, 3.7 \pm 0.15$ @ 25.00 °C	633	[20] , [21]
carboxyfluorescein	3.2	488	
Alexa-488	$1.96, 4.35$ @ 22.5 ± 0.5 °C	488	[22] [23]
Atto655-maleimide	4.07 ± 0.1 @ 25.00 °C	663	[24]
Atto655-carboxylic acid	4.26 ± 0.08 @ 25.00 °C	663	[25]
2', 7'-difluorofluorescein (Oregon Green488)	4.11 ± 0.06 @ 25.00 °C	498	[26]

Variations of FCS

FCS almost always refers to the single point, single channel, temporal autocorrelation measurement, although the term "fluorescence correlation spectroscopy" out of its historical scientific context implies no such restriction. FCS has been extended in a number of variations by different researchers, with each extension generating another name (usually an acronym).

Fluorescence cross-correlation spectroscopy (FCCS)

FCS is sometimes used to study molecular interactions using differences in diffusion times (e.g. the product of an association reaction will be larger and thus have larger diffusion times than the reactants individually); however, FCS is relatively insensitive to molecular mass as can be seen from the following equation relating molecular mass to the diffusion time of globular particles (e.g. proteins):

$$\tau_D = \frac{3\pi\omega_{xy}^2\eta}{2kT}(M)^{1/3}$$

where η is the viscosity of the sample and M is the molecular mass of the fluorescent species. In practice, the diffusion times need to be sufficiently different—a factor of at least **1.6**—which means the molecular masses must differ by a factor of **4**.^[27] Dual color fluorescence cross-correlation spectroscopy (FCCS) measures interactions by cross-correlating two or more fluorescent channels (one channel for each reactant), which distinguishes interactions more sensitively than FCS, particularly when the mass change in the reaction is small.

Brightness analysis methods (N&B,^[28] PCH,^[29] FIDA,^[30] Cumulant Analysis^[31])

Fluorescence cross correlation spectroscopy overcomes the weak dependence of diffusion rate on molecular mass by looking at multicolor coincidence. What about homo-interactions? The solution lies in brightness analysis. These methods use the heterogeneity in the intensity distribution of fluorescence to measure the molecular brightness of different species in a sample. Since dimers will contain twice the number of fluorescent labels as monomers, their molecular brightness will be approximately double that of monomers. As a result, the relative brightness is sensitive a measure of oligomerization. The average molecular brightness ($\langle\epsilon\rangle$) is related to the variance (σ^2) and the average intensity ($\langle I \rangle$) as follows:^[32]

$$\langle\epsilon\rangle = \frac{\sigma^2 - \langle I \rangle}{\langle I \rangle} = \sum_i f_i \epsilon_i$$

Here f_i and ϵ_i are the fractional intensity and molecular brightness, respectively, of species i .

Two- and three- photon FCS excitation

Several advantages in both spatial resolution and minimizing photodamage/photobleaching in organic and/or biological samples are obtained by two-photon or three-photon excitation FCS^{[33] [34] [35] [36] [37]}.

FRET-FCS

Another FCS based approach to studying molecular interactions uses fluorescence resonance energy transfer (FRET) instead of fluorescence, and is called FRET-FCS.^[38] With FRET, there are two types of probes, as with FCCS; however, there is only one channel and light is only detected when the two probes are very close—close enough to ensure an interaction. The FRET signal is weaker than with fluorescence, but has the advantage that there is only signal during a reaction (aside from autofluorescence).

Image correlation spectroscopy (ICS)

When the motion is slow (in biology, for example, diffusion in a membrane), getting adequate statistics from a single-point FCS experiment may take a prohibitively long time. More data can be obtained by performing the experiment in multiple spatial points in parallel, using a laser scanning confocal microscope. This approach has been called Image Correlation Spectroscopy (ICS)^[39]. The measurements can then be averaged together.

Another variation of ICS performs a spatial autocorrelation on images, which gives information about the concentration of particles^[40]. The correlation is then averaged in time.

A natural extension of the temporal and spatial correlation versions is spatio-temporal ICS (STICS)^[41]. In STICS there is no explicit averaging in space or time (only the averaging inherent in correlation). In systems with non-isotropic motion (e.g. directed flow, asymmetric diffusion), STICS can extract the directional information. A variation that is closely related to STICS (by the Fourier transform) is *k*-space Image Correlation Spectroscopy (kICS).^[42]

There are cross-correlation versions of ICS as well.^[39]

Scanning FCS variations

Some variations of FCS are only applicable to serial scanning laser microscopes. Image Correlation Spectroscopy and its variations all were implemented on a scanning confocal or scanning two photon microscope, but transfer to other microscopes, like a spinning disk confocal microscope. Raster ICS (RICS)^[43], and position sensitive FCS (PSFCS)^[44] incorporate the time delay between parts of the image scan into the analysis. Also, low dimensional scans (e.g. a circular ring)^[45]—only possible on a scanning system—can access time scales between single point and full image measurements. Scanning path has also been made to adaptively follow particles.^[46]

Spinning disk FCS, and spatial mapping

Any of the image correlation spectroscopy methods can also be performed on a spinning disk confocal microscope, which in practice can obtain faster imaging speeds compared to a laser scanning confocal microscope. This approach has recently been applied to diffusion in a spatially varying complex environment, producing a pixel resolution map of a diffusion coefficient.^[47] The spatial mapping of diffusion with FCS has subsequently been extended to the TIRF system.^[48] Spatial mapping of dynamics using correlation techniques had been applied before, but only at sparse points^[49] or at coarse resolution^[41].

Total internal reflection FCS

Total internal reflection fluorescence (TIRF) is a microscopy approach that is only sensitive to a thin layer near the surface of a coverslip, which greatly minimizes background fluorescence. FCS has been extended to that type of microscope, and is called TIR-FCS^[50]. Because the fluorescence intensity in TIRF falls off exponentially with distance from the coverslip (instead of as a Gaussian with a confocal), the autocorrelation function is different.

Other fluorescent dynamical approaches

There are two main non-correlation alternatives to FCS that are widely used to study the dynamics of fluorescent species.

Fluorescence recovery after photobleaching (FRAP)

In FRAP, a region is briefly exposed to intense light, irrecoverably photobleaching fluorophores, and the fluorescence recovery due to diffusion of nearby (non-bleached) fluorophores is imaged. A primary advantage of FRAP over FCS is the ease of interpreting qualitative experiments common in cell biology. Differences between cell lines, or regions of a cell, or before and after application of drug, can often be characterized by simple inspection of movies. FCS experiments require a level of processing and are more sensitive to potentially confounding influences like: rotational diffusion, vibrations, photobleaching, dependence on illumination and fluorescence color, inadequate statistics, etc. It is much easier to change the measurement volume in FRAP, which allows greater control. In practice, the volumes are typically larger than in FCS. While FRAP experiments are typically more qualitative, some researchers are studying FRAP quantitatively and including binding dynamics.^[51] A disadvantage of FRAP in cell biology is the free radical perturbation of the cell caused by the photobleaching. It is also less versatile, as it cannot measure concentration or rotational diffusion, or co-localization. FRAP requires a significantly higher concentration of fluorophores than FCS.

Particle tracking

In particle tracking, the trajectories of a set of particles are measured, typically by applying particle tracking algorithms to movies.^[52] Particle tracking has the advantage that all the dynamical information is maintained in the measurement, unlike FCS where correlation averages the dynamics to a single smooth curve. The advantage is apparent in systems showing complex diffusion, where directly computing the mean squared displacement allows straightforward comparison to normal or power law diffusion. To apply particle tracking, the particles have to be distinguishable and thus at lower concentration than required of FCS. Also, particle tracking is more sensitive to noise, which can sometimes affect the results unpredictably.

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External links

- Single-molecule spectroscopic methods (<http://dx.doi.org/10.1016/j.sbi.2004.09.004>)
- FCS Classroom (<http://www.fcsxpert.com/classroom>)
- Stowers Institute FCS Tutorial (<http://research.stowers-institute.org/microscopy/external/Technology/FCS/index.htm>)
- Cell Migration Consortium FCS Tutorial (http://www.cellmigration.org/resource/imaging/imaging_approaches_correlation_microscopy.shtml)

Fluorescence cross-correlation spectroscopy

Fluorescence cross-correlation spectroscopy (FCCS) was introduced by Eigen and Rigler in 1994 and experimentally realized by Schwille in 1997. It extends the fluorescence correlation spectroscopy (FCS) procedure by introducing high sensitivity for distinguishing fluorescent particles which have a similar diffusion coefficient. FCCS uses two species which are independently labelled with two spectrally separated fluorescent probes. These fluorescent probes are excited and detected by two different laser light sources and detectors commonly known as green and red respectively. Both laser light beams are focused into the sample and tuned so that they overlap to form a superimposed confocal observation volume.

The normalized cross-correlation function is defined for two fluorescent species G and R which are independent green, G and red, R channels as follows:

$$G_{GR}(\tau) = 1 + \frac{\langle \delta I_G(t) \delta I_R(t + \tau) \rangle}{\langle I_G(t) \rangle \langle I_R(t) \rangle} = \frac{\langle I_G(t) I_R(t + \tau) \rangle}{\langle I_G(t) \rangle \langle I_R(t) \rangle}$$

where differential fluorescent signals δI_G at a specific time, t and δI_R at a delay time, τ later is correlated with each other.

Modeling

Cross-correlation curves are modeled according to a slightly more complicated mathematical function than applied in FCS. First of all, the effective superimposed observation volume in which the G and R channels form a single observation volume, $V_{eff,RG}$ in the solution:

$$V_{eff,RG} = \pi^{3/2}(\omega_{xy,G}^2 + \omega_{xy,R}^2)(\omega_{z,G}^2 + \omega_{z,R}^2)^{1/2}/2^{3/2}$$

where $\omega_{xy,G}^2$ and $\omega_{xy,R}^2$ are radial parameters and $\omega_{z,G}$ and $\omega_{z,R}$ are the axial parameters for the G and R channels respectively.

The diffusion time, $\tau_{D,GR}$ for a doubly (G and R) fluorescent species is therefore described as follows:

$$\tau_{D,GR} = \frac{\omega_{xy,G}^2 + \omega_{xy,R}^2}{8D_{GR}}$$

where D_{GR} is the diffusion coefficient of the doubly fluorescent particle.

The cross-correlation curve generated from diffusing doubly labelled fluorescent particles can be modelled in separate channels as follows:

$$G_G(\tau) = 1 + \frac{(\langle C_G \rangle Diff_k(\tau) + \langle C_{GR} \rangle Diff_k(\tau))}{V_{eff,GR}(\langle C_G \rangle + \langle C_{GR} \rangle)^2}$$

$$G_R(\tau) = 1 + \frac{(\langle C_R \rangle Diff_k(\tau) + \langle C_{GR} \rangle Diff_k(\tau))}{V_{eff,GR}(\langle C_R \rangle + \langle C_{GR} \rangle)^2}$$

In the ideal case, the cross-correlation function is proportional to the concentration of the doubly labeled fluorescent complex:

$$G_{GR}(\tau) = 1 + \frac{\langle C_{GR} \rangle Diff_{GR}(\tau)}{V_{eff}(\langle C_G \rangle + \langle C_{GR} \rangle)(\langle C_R \rangle + \langle C_{GR} \rangle)}$$

$$\text{with } Diff_k(\tau) = \frac{1}{(1 + \frac{\tau}{\tau_{D,i}})(1 + a^{-2}(\frac{\tau}{\tau_{D,i}})^{1/2})}$$

Contrary to FCS, the intercept of the cross-correlation curve does not yield information about the doubly labelled fluorescent particles in solution.

Fourier transform infrared spectroscopy

Fourier transform infrared spectroscopy (FTIR)^[1] is a technique which is used to obtain an infrared spectrum of absorption, emission, photoconductivity or Raman scattering of a solid, liquid or gas. An FTIR spectrometer simultaneously collects spectral data in a wide spectral range. This confers a significant advantage over a dispersive spectrometer which measures intensity over a narrow range of wavelengths at a time. FTIR technique has made dispersive infrared spectrometers all but obsolete (except sometimes in the near infrared) and opened up new applications of infrared spectroscopy.

The term *Fourier transform infrared spectroscopy* originates from the fact that a Fourier transform (a mathematical algorithm) is required to convert the raw data into the actual spectrum. For other uses of this kind of technique, see Fourier transform spectroscopy.

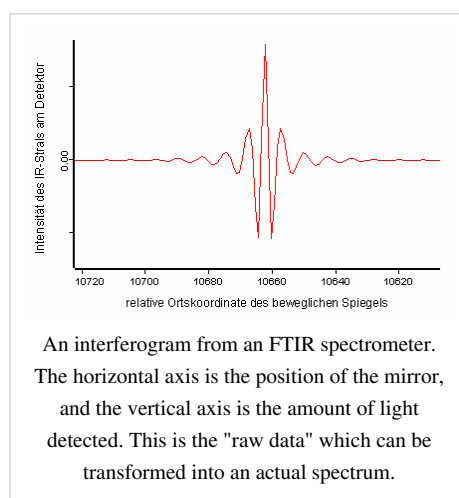
Conceptual introduction

The goal of any absorption spectroscopy (FTIR, ultraviolet-visible ("UV-Vis") spectroscopy, etc.) is to measure how well a sample absorbs light at each wavelength. The most straightforward way to do this, the "dispersive spectroscopy" technique, is to shine a monochromatic light beam at a sample, measure how much of the light is absorbed, and repeat for each different wavelength. (This is how UV-Vis spectrometers work, for example.)

Fourier transform spectroscopy is a less intuitive way to obtain the same information. Rather than shining a *monochromatic* beam of light at the sample, this technique shines a beam containing many different frequencies of light at once, and measures how much of that beam is absorbed by the sample. Next, the beam is modified to contain a different combination of frequencies, giving a second data point. This process is repeated many times. Afterwards, a computer takes all this data and works backwards to infer what the absorption is at each wavelength.

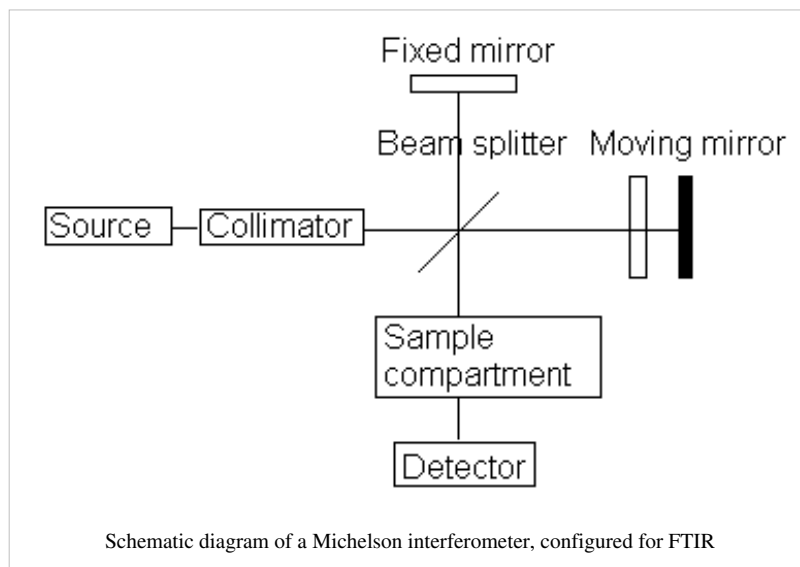
The beam described above is generated by starting with a broadband light source—one containing the full spectrum of wavelengths to be measured. The light shines into a certain configuration of mirrors, called a Michelson interferometer, that allows some wavelengths to pass through but blocks others (due to wave interference). The beam is modified for each new data point by moving one of the mirrors; this changes the set of wavelengths that pass through.

As mentioned, computer processing is required to turn the raw data (light absorption for each mirror position) into the desired result (light absorption for each wavelength). The processing required turns out to be a common algorithm called the Fourier transform (hence the name, "Fourier transform spectroscopy"). The raw data is sometimes called an "interferogram".



Michelson interferometer

In a Michelson interferometer adapted for FTIR, light from the polychromatic infrared source, approximately a black-body radiator, is collimated and directed to a beam splitter. Ideally 50% of the light is reflected towards the fixed mirror and 50% is transmitted towards the moving mirror. Light is reflected from the two mirrors back to the beam splitter and (ideally) 50% of the original light passes into the sample compartment. There, the light is focussed on the sample. On leaving the sample compartment the light is refocused on to the detector. The



difference in optical path length between the two arms to the interferometer is known as the retardation. An interferogram is obtained by varying the retardation and recording the signal from the detector for various values of the retardation. The form of the interferogram when no sample is present depends on factors such as the variation of source intensity and splitter efficiency with wavelength. This results in a maximum at zero retardation, when there is constructive interference at all wavelengths, followed by series of "wiggles". The position of zero retardation is determined accurately by finding the point of maximum intensity in the interferogram. When a sample is present the background interferogram is modulated by the presence of absorption bands in the sample.

There are two principle advantages for a FT spectrometer compared to a scanning (dispersive) spectrometer.^{[2] [3]}

1. The multiplex or Fellgett's advantage. This arises from the fact that information from all wavelengths is collected simultaneously. It results in a higher Signal-to-noise ratio for a given scan-time or a shorter scan-time for a given resolution.
2. The throughput or Jacquinot's advantage. This results from the fact that, in a dispersive instrument, the monochromator has entrance and exit slits which restrict the amount of light that passes through it. The interferometer throughput is determined only by the diameter of the collimated beam coming from the source.

Other minor advantages include less sensitivity to stray light,^[3] and "Connes' advantage" (better wavelength accuracy),^[3] while a disadvantage is that FTIR cannot use the advanced electronic filtering techniques that often makes its signal-to-noise ratio inferior to that of dispersive measurements.^[3]

Resolution

The interferogram belongs in the length domain. Fourier transform (FT) inverts the dimension, so the FT of the interferogram belongs in the reciprocal length domain, that is the wavenumber domain. The spectral resolution in wavenumbers per cm is equal to the reciprocal of the maximum retardation in cm. Thus a 4 cm^{-1} resolution will be obtained if the maximum retardation is 0.25 cm; this is typical of the cheaper FTIR instruments. Much higher resolution can be obtained by increasing the maximum retardation. This is not easy as the moving mirror must travel in a near-perfect straight line. The use of corner-cube mirrors in place of the flat mirrors is helpful as an outgoing ray from a corner-cube mirror is parallel to the incoming ray, regardless of the orientation of the mirror about axes perpendicular to the axis of the light beam. Connes measured in 1966 the temperature of the atmosphere of Venus by recording the vibration-rotation spectrum of Venusian CO_2 at 0.1 cm^{-1} resolution.^[4] Michelson himself attempted to resolve the hydrogen H_α emission band in the spectrum of a hydrogen atom into its two components by using his

interferometer.^{[1] p25} A spectrometer with 0.001 cm^{-1} resolution is now available commercially from Bruker. The throughput advantage is important for high-resolution FTIR as the monochromator in a dispersive instrument with the same resolution would have very narrow entrance and exit slits.

Beam splitter

The beam-splitter can not be made of a common glass, as it is opaque to infrared radiation of wavelengths longer than about $2.5\text{ }\mu\text{m}$. A thin film, usually of a plastic material, is used instead. However, as any material has a limited range of optical transmittance, several beam-splitters are used interchangeably to cover a wide spectral range.

Fourier transform

The interferogram in practice consists of a set of intensities measured for discrete values of retardation. The difference between successive retardation values is constant. Thus, a discrete Fourier transform is needed. The fast Fourier transform (FFT) algorithm is used.

Far-infrared FTIR

The first FTIR spectrometers were developed for far-infrared range. The reason for this has to do with the mechanical tolerance needed for good optical performance, which is related to the wavelength of the light being used. For the relatively long wavelengths of the far infrared ($\sim 10\text{ }\mu\text{m}$), tolerances are adequate, whereas for the rock-salt region tolerances have to be better than $1\text{ }\mu\text{m}$. A typical instrument was the cube interferometer developed at the NPL^[5] and marketed by Grubb Parsons. It used a stepper motor to drive the moving mirror, recording the detector response after each step was completed.

Mid-infrared FTIR

With the advent of cheap microcomputers it became possible to have a computer dedicated to controlling the spectrometer, collecting the data, doing the Fourier transform and presenting the spectrum. This provided the impetus for the development of FTIR spectrometers for the rock-salt region. The problems of manufacturing ultra-high precision optical and mechanical components had to be solved. A wide range of instruments is now available commercially. Although instrument design has become more sophisticated, the basic principles remain the same. Nowadays, the moving mirror of the interferometer moves at a constant velocity, and sampling of the interferogram is triggered by finding zero-crossings in the fringes of a secondary interferometer lit by a helium-neon laser. This confers high wavenumber accuracy on the resulting infrared spectrum and avoids wavenumber calibration errors.

Near-infrared FTIR

The near-infrared region spans the wavelength range between the rock-salt region and the start of the visible region at about 750 nm . Overtones of fundamental vibrations can be observed in this region. It is used mainly in industrial applications such as process control.

Applications

FTIR can be used in all applications where a dispersive spectrometer was used in the past (see external links). In addition, the multiplex and throughput advantages have opened up new areas of application. These include:

- GC-IR (gas chromatography-infrared spectrometry). A gas chromatograph can be used to separate the components of a mixture. The fractions containing single components are directed into an FTIR spectrometer, to provide the infrared spectrum of the sample. This technique is complementary to GC-MS (gas

chromatography-mass spectrometry). The GC-IR method is particularly useful for identifying isomers, which by their nature have identical masses. The key to the successful use of GC-IR is that the interferogram can be captured in a very short time, typically less than 1 second. FTIR has also been applied to the analysis of liquid chromatography fractions.^[3]

- TG-IR (thermogravimetry-infrared spectrometry) IR spectra of the gases evolved during thermal decomposition are obtained as a function of temperature.^[6]
- Micro-samples. Tiny samples, such as in forensic analysis, can be examined with the aid of an infrared microscope in the sample chamber. An image of the surface can be obtained by scanning.^[7] Another example is the use of FTIR to characterize artistic materials in old-master paintings.^[8]
- Emission spectra. Instead of recording the spectrum of light transmitted through the sample, FTIR spectrometer can be used to acquire spectrum of light emitted by the sample. Such emission could be induced by various processes, and the most common ones are luminescence and Raman scattering. Little modification is required to an absorption FTIR spectrometer to record emission spectra and therefore many commercial FTIR spectrometers combine both absorption and emission/Raman modes.^[9]
- Photocurrent spectra. This mode uses a standard, absorption FTIR spectrometer. The studied sample is placed instead of the FTIR detector, and its photocurrent, induced by the spectrometer's broadband source, is used to record the interferogram, which is then converted into the photoconductivity spectrum of the sample.^[10]

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External links

- Infracord spectrometer (<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC441765/pdf/jcinvest00449-0191.pdf>) photograph
- The Grubb-Parsons-NPL cube interferometer Spectroscopy, part 2 by Dudley Williams, page 81 (http://books.google.co.uk/books?id=XTolQEkzSR0C&pg=PA93&lpg=PA93&dq=grubb+parsons+cube&source=bl&ots=l0Sm8klxHG&sig=SzKdjgTB8YPyitRgAAIwH2zIOlo&hl=en&ei=w6lRTM-BNYaD4QaC48ygAw&sa=X&oi=book_result&ct=result&resnum=9&ved=0CDgQ6AEwCA#v=onepage&q=grubb+parsons+cube&f=false)
- FTIR application notes (<http://las.perkinelmer.com/Catalog/TechLibDetails.htm?expand=Application&20Notes&ObjectId=FTIR+&+FTNIR+Spectrometers&CategoryId=FTIR+&+FTNIR+Spectrometers&type=CATEGORY>) from Perkin Elmer

- FTIR application notes (<http://www.varianinc.com/cgi-bin/nav?applications/ftir&cid=LNHOMKLPFQ>) from Varian
- Infrared / FTIR Application Notes (<http://www.selectscience.net/infrared-+-ftir/application-notes>) Recent publications.
- Semiconductor applications (<http://www.piketech.com/technical/application-pdfs/SemiconductorApplOverview.pdf>) FTIR Sampling Techniques Overview.
- infrared materials (<http://infrared.als.lbl.gov/content/web-links/58-irwindows>) Properties of many salt crystals and useful links.

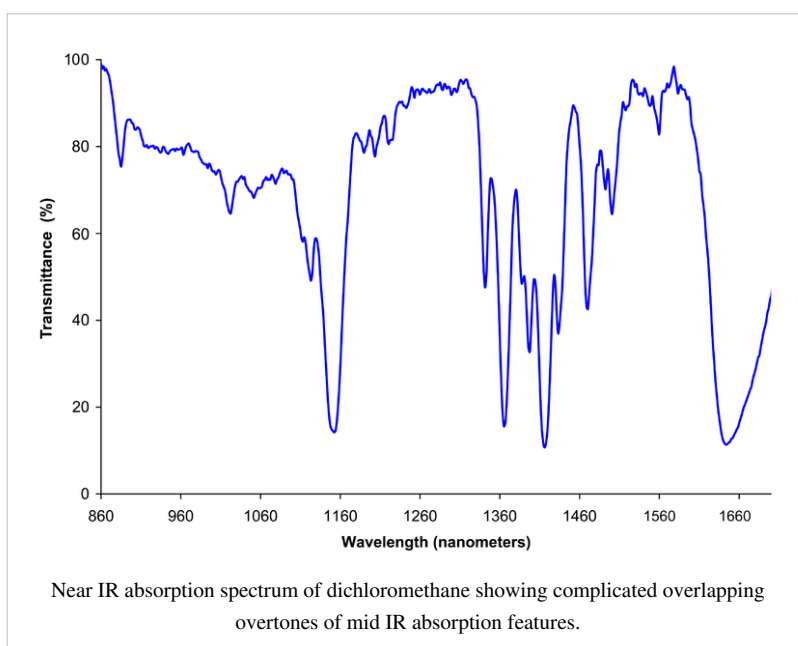
Near infrared spectroscopy

Near-infrared spectroscopy (NIRS) is a spectroscopic method that uses the near-infrared region of the electromagnetic spectrum (from about 800 nm to 2500 nm). Typical applications include pharmaceutical, medical diagnostics (including blood sugar and oximetry), food and agrochemical quality control, as well as combustion research.

Theory

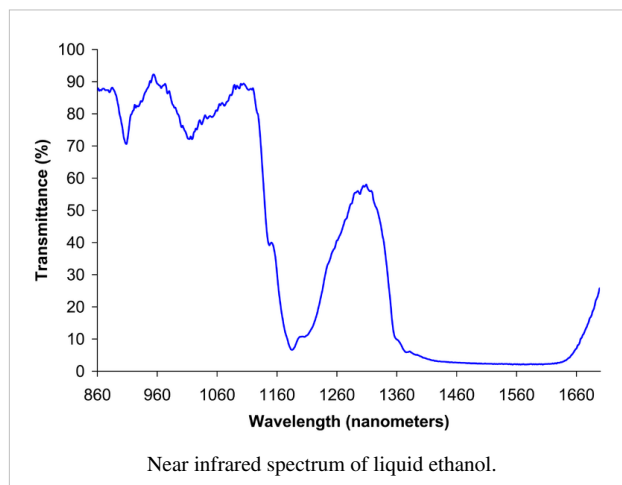
Near-infrared spectroscopy is based on molecular overtone and combination vibrations. Such transitions are forbidden by the selection rules of quantum mechanics. As a result, the molar absorptivity in the near IR region is typically quite small. One advantage is that NIR can typically penetrate much farther into a sample than mid infrared radiation. Near-infrared spectroscopy is, therefore, not a particularly sensitive technique, but it can be very useful in probing bulk material with little or no sample preparation.

The molecular overtone and combination bands seen in the near IR are typically very broad, leading to complex spectra; it can be difficult to assign specific features to specific chemical components. Multivariate (multiple wavelength) calibration techniques (e.g., principal components analysis, partial least squares, or artificial neural networks) are often employed to extract the desired chemical information. Careful development of a set of calibration samples and application of multivariate calibration techniques is essential for near-infrared analytical methods.^[1]



History

The discovery of near-infrared energy is ascribed to Herschel in the 19th century, but the first industrial application began in the 1950s. In the first applications, NIRS was used only as an add-on unit to other optical devices that used other wavelengths such as ultraviolet (UV), visible (Vis), or mid-infrared (MIR) spectrometers. In the 1980s, a single unit, stand-alone NIRS system was made available, but the application of NIRS was focused more on chemical analysis. With the introduction of light-fiber optics in the mid-1980s and the monochromator-detector developments in early-1990s, NIRS became a more powerful tool for scientific research.



This optical method can be used in a number of fields of science including physics, physiology, or medicine. It is only in the last few decades that NIRS began to be used as a medical tool for monitoring patients.

Instrumentation

Instrumentation for near-IR (NIR) spectroscopy is partially similar to instruments for the visible and mid-IR ranges. There is a source, a detector, and a dispersive element (such as a prism, or, more common, a diffraction grating) to allow the intensity at different wavelengths to be recorded. Fourier transform NIR instruments using an interferometer are also common, especially for wavelengths above ~1000 nm. Depending on the sample, the spectrum can be measured in either reflection or transmission.

Common incandescent or quartz halogen light bulbs are most often used as broadband sources of near-infrared radiation for analytical applications. Light-emitting diodes (LEDs) are also used; they offer greater lifetime and spectral stability and reduced power requirements.^[2]

The type of detector used depends primarily on the range of wavelengths to be measured. Silicon-based CCDs are suitable for the shorter end of the NIR range, but are not sufficiently sensitive over most of the range. InGaAs and PbS devices are more suitable. In certain diode array (DA) NIRS instruments, both silicon-based and InGaAs detectors are employed in the same instrument. Such instruments can record both visible and NIR spectra 'simultaneously'.

Instruments intended for chemical imaging in the NIR may use a 2D array detector with a acousto-optic tunable filter. Multiple images may be recorded sequentially at different narrow wavelength bands.^[3]

Many commercial instruments for UV/vis spectroscopy are capable of recording spectra in the NIR range (to perhaps ~900 nm). In the same way, the range of some mid-IR instruments may extend into the NIR. In these instruments, the detector used for the NIR wavelengths is often the same detector used for the instrument's "main" range of interest.

Applications

The primary application of NIRS to the human body uses the fact that the transmission and absorption of NIR light in human body tissues contains information about hemoglobin concentration changes. When a specific area of the brain is activated, the localized blood volume in that area changes quickly. Optical imaging can measure the location and activity of specific regions of the brain by continuously monitoring blood hemoglobin levels through the determination of optical absorption coefficients.

Typical applications of NIR spectroscopy include the analysis of foodstuffs, pharmaceuticals, combustion products and a major branch of astronomical spectroscopy.



NIR sensor for moisture measurement installed on a belt conveyor

Astronomical spectroscopy

Near-infrared spectroscopy is used in astronomy for studying the atmospheres of cool stars where molecules can form. The vibrational and rotational signatures of molecules such as titanium oxide, cyanide, and carbon monoxide can be seen in this wavelength range and can give a clue towards the star's spectral type. It is also used for studying molecules in other astronomical contexts, such as in molecular clouds where new stars are formed. The astronomical phenomenon known as reddening means that near-infrared wavelengths are less affected by dust in the interstellar medium, such that regions inaccessible by optical spectroscopy can be studied in the near-infrared. Since dust and gas are strongly associated, these dusty regions are exactly those where infrared spectroscopy is most useful. The near-infrared spectra of very young stars provide important information about their ages and masses, which is important for understanding star formation in general.

Remote monitoring

Techniques have been developed for NIR spectroscopic imaging. These have been used for a wide range of uses, including the remote investigation of plants and soils. Data can be collected from instruments on airplanes or satellites to assess ground cover and soil chemistry.

Medical uses

Medical applications of NIRS center on the non-invasive measurement of the amount and oxygen content of hemoglobin, as well as the use of exogenous optical tracers in conjunction with flow kinetics.

NIRS can be used for non-invasive assessment of brain function through the intact skull in human subjects by detecting changes in blood hemoglobin concentrations associated with neural activity, e.g., in branches of Cognitive psychology as a partial replacement for fMRI techniques. NIRS can be used on infants, where fMRI cannot (at least in the United States), and NIRS is much more portable than fMRI machines, even wireless instrumentation is available, which enables investigations in freely moving subjects^[4]). However, NIRS cannot fully replace fMRI because it can only be used to scan cortical tissue, where fMRI can be used to measure activation throughout the brain.

The application in functional mapping of the human cortex is called optical topography (OT), near infrared imaging (NIRI) or functional NIRS (fNIRS). The term optical tomography is used for three-dimensional NIRS. The terms NIRS, NIRI and OT are often used interchangeably, but they have some distinctions. The most important difference between NIRS and OT/NIRI is that OT/NIRI is used mainly to detect changes in optical properties of tissue simultaneously from multiple measurement points and display the results in the form of a map or image over a specific area, whereas NIRS provides quantitative data in absolute terms on up to a few specific points. The latter is

also used to investigate other tissues such as, e.g., muscle, breast and tumors.

By employing several wavelengths and time resolved (frequency or time domain) and/or spatially resolved methods blood flow, volume and oxygenation can be quantified^[5]. These measurements are a form of oximetry. Applications of oximetry by NIRS methods include the detection of illnesses which affect the blood circulation (e.g., peripheral vascular disease), the detection and assessment of breast tumors, and the optimization of training in sports medicine. These techniques can also be used for industry or agro processes in order to predict particle size/density.

The use of NIRS in conjunction with a bolus injection of indocyanine green (ICG) has been used to measure cerebral blood flow^[6] and cerebral metabolic rate of oxygen consumption^[7] in neonatal models.

NIRS is starting to be used in pediatric critical care, to help deal with cardiac surgery post-op. Indeed, NIRS is able to measure venous oxygen saturation (SVO₂), which is determined by the cardiac output, as well as other parameters (FiO₂, hemoglobin, oxygen uptake). Therefore, following the NIRS gives critical care physicians a notion of the cardiac output. NIRS is liked by patients, because it is non-invasive, is painless, and uses non-ionizing radiation.

The instrumental development of NIRS/NIRI/OT has proceeded tremendously during the last years and, in particular, in terms of quantification, imaging and miniaturization^[5].

Particle measurement

NIR is often used in particle sizing in a range of different fields, including studying pharmaceutical and agricultural powders.

Industrial uses

As opposed to NIRS used in optical topography, general NIRS used in chemical assays does not provide imaging by mapping. For example, a clinical carbon dioxide analyzer requires reference techniques and calibration routines to be able to get accurate CO₂ content change. In this case, calibration is performed by adjusting the zero control of the sample being tested after purposefully supplying 0% CO₂ or another known amount of CO₂ in the sample. Normal compressed gas from distributors contains about 95% O₂ and 5% CO₂, which can also be used to adjust %CO₂ meter reading to be exactly 5% at initial calibration.

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Infrared spectroscopy

Infrared spectroscopy (IR spectroscopy) is the spectroscopy that deals with the infrared region of the electromagnetic spectrum, that is light with a longer wavelength and lower frequency than visible light. It covers a range of techniques, mostly based on absorption spectroscopy. As with all spectroscopic techniques, it can be used to identify and study chemicals. A common laboratory instrument that uses this technique is a Fourier transform infrared (FTIR) spectrometer.

The infrared portion of the electromagnetic spectrum is usually divided into three regions; the near-, mid- and far-infrared, named for their relation to the visible spectrum. The higher energy near-IR, approximately $14000\text{--}4000\text{ cm}^{-1}$ ($0.8\text{--}2.5\text{ }\mu\text{m}$ wavelength) can excite overtone or harmonic vibrations. The mid-infrared, approximately $4000\text{--}400\text{ cm}^{-1}$ ($2.5\text{--}25\text{ }\mu\text{m}$) may be used to study the fundamental vibrations and associated rotational-vibrational structure. The far-infrared, approximately $400\text{--}10\text{ cm}^{-1}$ ($25\text{--}1000\text{ }\mu\text{m}$), lying adjacent to the microwave region, has low energy and may be used for rotational spectroscopy. The names and classifications of these subregions are conventions, and are only loosely based on the relative molecular or electromagnetic properties.

Theory

Infrared spectroscopy exploits the fact that molecules absorb specific frequencies that are characteristic of their structure. These absorptions are resonant frequencies, i.e. the frequency of the absorbed radiation matches the frequency of the bond or group that vibrates. The energies are determined by the shape of the molecular potential energy surfaces, the masses of the atoms, and the associated vibronic coupling.

In particular, in the Born–Oppenheimer and harmonic approximations, i.e. when the molecular Hamiltonian corresponding to the electronic ground state can be approximated by a harmonic oscillator in the neighborhood of the equilibrium molecular geometry, the resonant frequencies are determined by the normal modes corresponding to the molecular electronic ground state potential energy surface. Nevertheless, the resonant frequencies can be in a first approach related to the strength of the bond, and the mass of the atoms at either end of it. Thus, the frequency of the vibrations can be associated with a particular bond type.

Number of vibrational modes

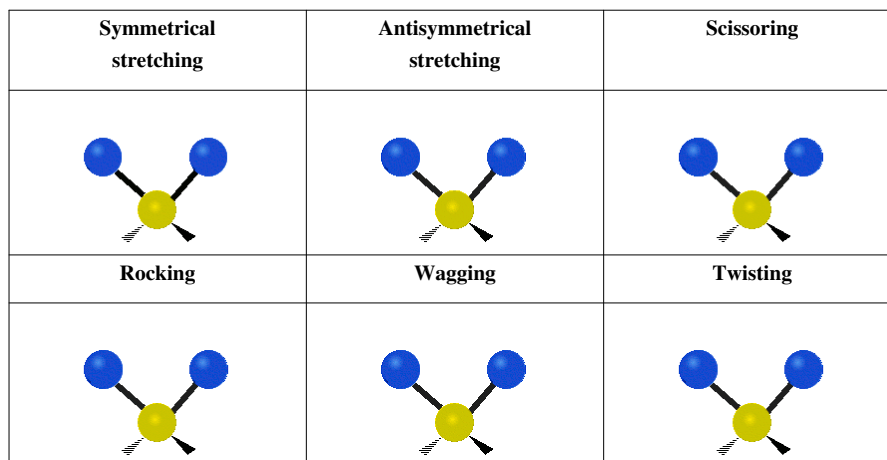
In order for a vibrational mode in a molecule to be "IR active," it must be associated with changes in the permanent dipole.

A molecule can vibrate in many ways, and each way is called a *vibrational mode*. Linear molecules have $3N - 5$ degrees of vibrational modes whereas nonlinear molecules have $3N - 6$ degrees of vibrational modes (also called vibrational degrees of freedom). As an example H_2O , a non-linear molecule, will have $3 \times 3 - 6 = 3$ degrees of vibrational freedom, or modes.

Simple diatomic molecules have only one bond and only one vibrational band. If the molecule is symmetrical, e.g. N_2 , the band is not observed in the IR spectrum, but only in the Raman spectrum. Unsymmetrical diatomic molecules, e.g. CO, absorb in the IR spectrum. More complex molecules have many bonds, and their vibrational

spectra are correspondingly more complex, i.e. big molecules have many peaks in their IR spectra.

The atoms in a CH_2 group, commonly found in organic compounds, can vibrate in six different ways: **symmetric and antisymmetric stretching, scissoring, rocking, wagging and twisting**:



(These figures do not represent the "recoil" of the C atoms, which, though necessarily present to balance the overall movements of the molecule, are much smaller than the movements of the lighter H atoms).

Special effects

The simplest and most important IR bands arise from the "normal modes," the simplest distortions of the molecule. In some cases, "overtone bands" are observed. These bands arise from the absorption of a photon that leads to a doubly excited vibrational state. Such bands appear at approximately twice the energy of the normal mode. Some vibrations, so-called 'combination modes,' involve more than one normal mode. The phenomenon of Fermi resonance can arise when two modes are similar in energy, Fermi resonance results in an unexpected shift in energy and intensity of the bands.

Practical IR spectroscopy

The infrared spectrum of a sample is recorded by passing a beam of infrared light through the sample. Examination of the transmitted light reveals how much energy was absorbed at each wavelength. This can be done with a monochromatic beam, which changes in wavelength over time, or by using a Fourier transform instrument to measure all wavelengths at once. From this, a transmittance or absorbance spectrum can be produced, showing at which IR wavelengths the sample absorbs. Analysis of these absorption characteristics reveals details about the molecular structure of the sample. When the frequency of the IR is the same as the vibrational frequency of a bond, absorption occurs.

This technique works almost exclusively on samples with covalent bonds. Simple spectra are obtained from samples with few IR active bonds and high levels of purity. More complex molecular structures lead to more absorption bands and more complex spectra. The technique has been used for the characterization of very complex mixtures.

Sample preparation

Gaseous samples require a sample cell with a long pathlength (typically 5–10 cm), to compensate for the diluteness.

Liquid samples can be sandwiched between two plates of a salt (commonly sodium chloride, or common salt, although a number of other salts such as potassium bromide or calcium fluoride are also used).^[1] The plates are transparent to the infrared light and do not introduce any lines onto the spectra.

Solid samples can be prepared in a variety of ways. One common method is to crush the sample with an oily mulling agent (usually Nujol) in a marble or agate mortar, with a pestle. A thin film of the mull is smeared onto salt plates and measured. The second method is to grind a quantity of the sample with a specially purified salt (usually potassium bromide) finely (to remove scattering effects from large crystals). This powder mixture is then pressed in a mechanical press to form a translucent pellet through which the beam of the spectrometer can pass.^[1] A third technique is the "cast film" technique, which is used mainly for polymeric materials. The sample is first dissolved in a suitable, non hygroscopic solvent. A drop of this solution is deposited on surface of KBr or NaCl cell. The solution is then evaporated to dryness and the film formed on the cell is analysed directly. Care is important to ensure that the film is not too thick otherwise light cannot pass through. This technique is suitable for qualitative analysis. The final method is to use microtomy to cut a thin (20–100 μm) film from a solid sample. This is one of the most important ways of analysing failed plastic products for example because the integrity of the solid is preserved.

It is important to note that spectra obtained from different sample preparation methods will look slightly different from each other due to differences in the samples' physical states.

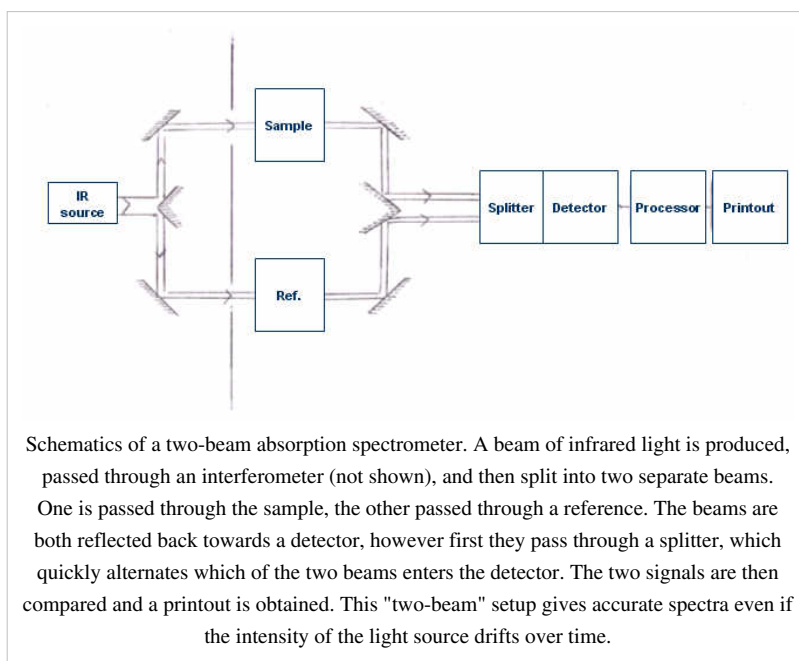
Comparing to a reference

To take the infrared spectrum of a sample, it is necessary to measure both the sample and a "reference" (or "control"). This is because each measurement is affected by not only the light-absorption properties of the sample, but also the properties of the instrument (for example, what light source is used, what detector is used, etc.). The reference measurement makes it possible to eliminate the instrument influence. Mathematically, the sample transmission spectrum is divided by the reference transmission spectrum.

The appropriate "reference" depends on the measurement and its goal. The simplest reference measurement is to simply remove the sample (replacing it by air). However, sometimes a different reference is more useful. For example, if the sample is a dilute solute dissolved in water in a beaker, then a good reference measurement might be to measure pure water in the same beaker. Then the reference measurement would cancel out not only all the instrumental properties (like what light source is used), but also the light-absorbing and light-reflecting properties of the water and beaker, and the final result would just show the properties of the solute (at least approximately).

The simplest reference measurement is to simply remove the sample (replacing it by air). However, sometimes a different reference is more useful. For example, if the sample is a dilute solute dissolved in water in a beaker, then a good reference measurement might be to measure pure water in the same beaker. Then the reference measurement would cancel out not only all the instrumental properties (like what light source is used), but also the light-absorbing and light-reflecting properties of the water and beaker, and the final result would just show the properties of the solute (at least approximately).

A common way to compare to a reference is sequentially: First measure the reference, then replace the reference by the sample, then measure the sample. This technique is not perfectly reliable: If the infrared lamp is a bit brighter

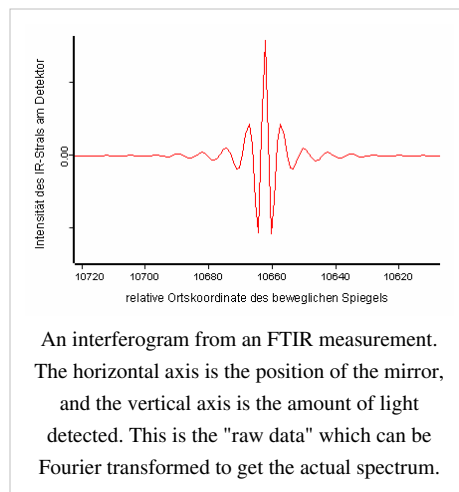


during the reference measurement, then a bit dimmer during the sample measurement, the measurement will be distorted. More elaborate methods, such as a "two-beam" setup (see figure), can correct for these types of effects to give very accurate results.

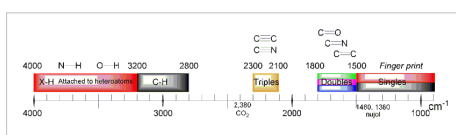
FTIR

Fourier transform infrared (FTIR) spectroscopy is a measurement technique that allows one to record infrared spectra. Infrared light is guided through an interferometer and then through the sample (or vice versa). A moving mirror inside the apparatus alters the distribution of infrared light that passes through the interferometer. The signal directly recorded, called an "interferogram", represents light output as a function of mirror position. A data-processing technique called Fourier transform turns this raw data into the desired result (the sample's spectrum): Light output as a function of infrared wavelength (or equivalently, wavenumber). As described above, the sample's spectrum is always compared to a reference.

There is an alternate method for taking spectra (the "dispersive" or "scanning monochromator" method), where one wavelength at a time passes through the sample. The dispersive method is more common in UV-Vis spectroscopy, but is less practical in the infrared than the FTIR method. One reason that FTIR is favored is called " Fellgett's advantage" or the "multiplex advantage": The information at all frequencies is collected simultaneously, improving both speed and signal-to-noise ratio. Another is called "Jacquinot's Throughput Advantage": A dispersive measurement requires detecting much lower light levels than an FTIR measurement.^[2] There are other advantages, as well as some disadvantages,^[2] but virtually all modern infrared spectrometers are FTIR instruments.



Absorption bands



Wavenumbers listed in cm^{-1} .

Uses and applications

Infrared spectroscopy is widely used in both research and industry as a simple and reliable technique for measurement, quality control and dynamic measurement. It is also used in forensic analysis in both criminal and civil cases, enabling identification of polymer degradation for example.

The instruments are now small, and can be transported, even for use in field trials. With increasing technology in computer filtering and manipulation of the results, samples in solution can now be measured accurately (water produces a broad absorbance across the range of interest, and thus renders the spectra unreadable without this computer treatment). Some instruments will also automatically tell you what substance is being measured from a store of thousands of reference spectra held in storage.

By measuring at a specific frequency over time, changes in the character or quantity of a particular bond can be measured. This is especially useful in measuring the degree of polymerization in polymer manufacture. Modern research instruments can take infrared measurements across the whole range of interest as frequently as 32 times a

second. This can be done whilst simultaneous measurements are made using other techniques. This makes the observations of chemical reactions and processes quicker and more accurate.

Infrared spectroscopy has been highly successful for applications in both organic and inorganic chemistry. Infrared spectroscopy has also been successfully utilized in the field of semiconductor microelectronics.^[3] for example, infrared spectroscopy can be applied to semiconductors like silicon, gallium arsenide, gallium nitride, zinc selenide, amorphous silicon, silicon nitride, etc.

Isotope effects

The different isotopes in a particular species may give fine detail in infrared spectroscopy. For example, the O–O stretching frequency (in reciprocal centimeters) of oxyhemocyanin is experimentally determined to be 832 and 788 cm^{−1} for $\nu(^{16}\text{O}-^{16}\text{O})$ and $\nu(^{18}\text{O}-^{18}\text{O})$, respectively.

By considering the O–O bond as a spring, the wavenumber of absorbance, ν can be calculated:

$$\nu = \frac{1}{2\pi c} \sqrt{\frac{k}{\mu}}$$

where k is the spring constant for the bond, c is the speed of light, and μ is the reduced mass of the A–B system:

$$\mu = \frac{m_A m_B}{m_A + m_B}$$

(m_i is the mass of atom i).

The reduced masses for $^{16}\text{O}-^{16}\text{O}$ and $^{18}\text{O}-^{18}\text{O}$ can be approximated as 8 and 9 respectively. Thus

$$\frac{\nu(^{16}\text{O})}{\nu(^{18}\text{O})} = \sqrt{\frac{9}{8}} \approx \frac{832}{788}.$$

Where ν is the wavenumber; [wavenumber = frequency/(speed of light)]

The effect of isotopes, both on the vibration and the decay dynamics, has been found to be stronger than previously thought. In some systems, such as silicon and germanium, the decay of the anti-symmetric stretch mode of interstitial oxygen involves the symmetric stretch mode with a strong isotope dependence. For example, it was shown that for a natural silicon sample, the lifetime of the anti-symmetric vibration is 11.4 ps. When the isotope of one of the silicon atoms is increased to ^{29}Si , the lifetime increases to 19 ps. In similar manner, when the silicon atom is changed to ^{30}Si , the lifetime becomes 27 ps.^[4]

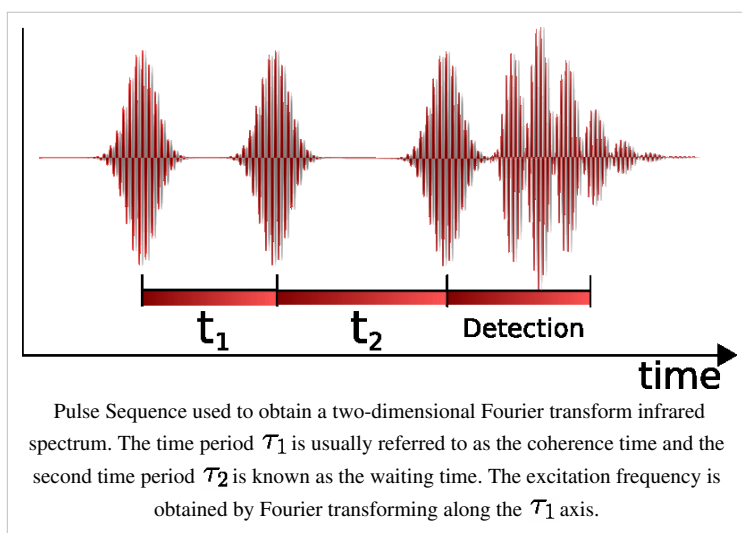
Two-dimensional IR

Two-dimensional infrared correlation spectroscopy analysis is the application of 2D correlation analysis on infrared spectra. By extending the spectral information of a perturbed sample, spectral analysis is simplified and resolution is enhanced. The 2D synchronous and 2D asynchronous spectra represent a graphical overview of the spectral changes due to a perturbation (such as a changing concentration or changing temperature) as well as the relationship between the spectral changes at two different wavenumbers.

Nonlinear two-dimensional infrared spectroscopy^{[5] [6]}

is the infrared version of correlation spectroscopy. Nonlinear two-dimensional infrared spectroscopy is a technique that has become available with the development of femtosecond infrared laser pulses. In this experiment, first a set of pump pulses are applied to the sample. This is followed by a waiting time, wherein the system is allowed to relax. The typical waiting time lasts from zero to several picoseconds, and the duration can be controlled with a resolution of tens of femtoseconds. A probe pulse is then applied

resulting in the emission of a signal from the sample. The nonlinear two-dimensional infrared spectrum is a two-dimensional correlation plot of the frequency ω_1 that was excited by the initial pump pulses and the frequency ω_3 excited by the probe pulse after the waiting time. This allows the observation of coupling between different vibrational modes; because of its extremely high time resolution, it can be used to monitor molecular dynamics on a picosecond timescale. It is still a largely unexplored technique and is becoming increasingly popular for fundamental research.



As with two-dimensional nuclear magnetic resonance (2DNMR) spectroscopy, this technique spreads the spectrum in two dimensions and allows for the observation of cross peaks that contain information on the coupling between different modes. In contrast to 2DNMR, nonlinear two-dimensional infrared spectroscopy also involves the excitation to overtones. These excitations result in excited state absorption peaks located below the diagonal and cross peaks. In 2DNMR, two distinct techniques, COSY and NOESY, are frequently used. The cross peaks in the first are related to the scalar coupling, while in the later they are related to the spin transfer between different nuclei. In nonlinear two-dimensional infrared spectroscopy, analogs have been drawn to these 2DNMR techniques. Nonlinear two-dimensional infrared spectroscopy with zero waiting time corresponds to COSY, and nonlinear two-dimensional infrared spectroscopy with finite waiting time allowing vibrational population transfer corresponds to NOESY. The COSY variant of nonlinear two-dimensional infrared spectroscopy has been used for determination of the secondary structure content proteins.^[7]

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External links

- A useful gif animation of different vibrational modes: SHU.ac.uk (<http://www.shu.ac.uk/schools/sci/chem/tutorials/molspec/irspec1.htm>)
- Infrared spectroscopy for organic chemists (<http://www.dq.fct.unl.pt/qoa/jas/ir.html>)
- Organic compounds spectrum database (http://riodb01.ibase.aist.go.jp/sdbs/cgi-bin/cre_index.cgi?lang=eng)

Vibrational spectroscopy

A **molecular vibration** occurs when atoms in a molecule are in periodic motion while the molecule as a whole has constant translational and rotational motion. The frequency of the periodic motion is known as a vibration frequency. The three atomic molecule have three modes of vibration irrespective of whether these are linear or nonlinear. The molecules with n (n must be greater than 3) atoms has $3n-6$ normal modes of vibration, whereas a *linear* molecule has $3n-5$ normal modes of vibration because rotation about its molecular axis is simply a rotation of the reference frame and cannot be observed^[1]. A diatomic molecule thus has only one normal mode of vibration. The normal modes of vibration of polyatomic molecules are independent of each other, each involving simultaneous vibrations of different parts of the molecule.

A molecular vibration is excited when the molecule absorbs a quantum of energy, E , corresponding to the vibration's frequency, ν , according to the relation $E=h\nu$, where h is Planck's constant. A fundamental vibration is excited when one such quantum of energy is absorbed by the molecule in its ground state. When two quanta are absorbed the first overtone is excited, and so on to higher overtones.

To a first approximation, the motion in a normal vibration can be described as a kind of simple harmonic motion. In this approximation, the vibrational energy is a quadratic function (parabola) with respect to the atomic displacements and the first overtone has twice the frequency of the fundamental. In reality, vibrations are anharmonic and the first overtone has a frequency that is slightly lower than twice that of the fundamental. Excitation of the higher overtones involves progressively less and less additional energy and eventually leads to dissociation of the molecule, as the potential energy of the molecule is more like a Morse potential.

The vibrational states of a molecule can be probed in a variety of ways. The most direct way is through infrared spectroscopy, as vibrational transitions typically require an amount of energy that corresponds to the infrared region of the spectrum. Raman spectroscopy, which typically uses visible light, can also be used to measure vibration frequencies directly.

Vibrational excitation can occur in conjunction with electronic excitation (vibronic transition), giving vibrational fine structure to electronic transitions, particularly with molecules in the gas state.

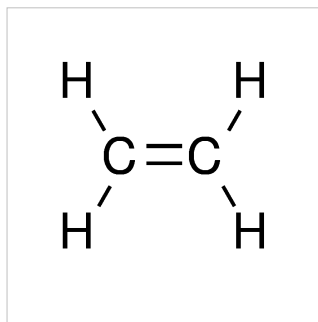
Simultaneous excitation of a vibration and rotations gives rise to vibration-rotation spectra.

Vibrational coordinates

The coordinate of a normal vibration is a combination of *changes* in the positions of atoms in the molecule. When the vibration is excited the coordinate changes sinusoidally with a frequency ν , the frequency of the vibration.

Internal coordinates

Internal coordinates are of the following types, illustrated with reference to the planar molecule ethylene,



- Stretching: a change in the length of a bond, such as C-H or C-C
- Bending: a change in the angle between two bonds, such as the HCH angle in a methylene group
- Rocking: a change in angle between a group of atoms, such as a methylene group and the rest of the molecule.
- Wagging: a change in angle between the plane of a group of atoms, such as a methylene group and a plane through the rest of the molecule,
- Twisting: a change in the angle between the planes of two groups of atoms, such as a change in the angle between the two methylene groups.
- Out-of-plane: a change in the angle between any one of the C-H bonds and the plane defined by the remaining atoms of the ethylene molecule. Another example is in BF_3 when the boron atom moves in and out of the plane of the three fluorine atoms.

In a rocking, wagging or twisting coordinate the bond lengths within the groups involved do not change. The angles do. Rocking is distinguished from wagging by the fact that the atoms in the group stay in the same plane.

In ethene there are 12 internal coordinates: 4 C-H stretching, 1 C-C stretching, 2 H-C-H bending, 2 CH_2 rocking, 2 CH_2 wagging, 1 twisting. Note that the H-C-C angles cannot be used as internal coordinates as the angles at each carbon atom cannot all increase at the same time.

See infrared spectroscopy for some animated illustrations of internal coordinates.

Symmetry-adapted coordinates

Symmetry-adapted coordinates may be created by applying a projection operator to a set of internal coordinates.^[2] The projection operator is constructed with the aid of the character table of the molecular point group. For example, the four(un-normalised) C-H stretching coordinates of the molecule ethene are given by

$$Q_{s1} = q_1 + q_2 + q_3 + q_4$$

$$Q_{s2} = q_1 + q_2 - q_3 - q_4$$

$$Q_{s3} = q_1 - q_2 + q_3 - q_4$$

$$Q_{s4} = q_1 - q_2 - q_3 + q_4$$

where $q_1 - q_4$ are the internal coordinates for stretching of each of the four C-H bonds.

Illustrations of symmetry-adapted coordinates for most small molecules can be found in Nakamoto.^[3]

Normal coordinates

The normal coordinates, denoted as Q , refer to the positions of atoms away from their equilibrium positions, with respect to a normal mode of vibration. Each normal mode is assigned a single normal coordinate, and so the normal coordinate refers to the "progress" along that normal mode at any given time. Formally, normal modes are determined by solving a secular determinant, and then the normal coordinates (over the normal modes) can be expressed as a summation over the cartesian coordinates (over the atom positions). The advantage of working in normal modes is that they diagonalize the matrix governing the molecular vibrations, so each normal mode is an independent molecular vibration, associated with its own spectrum of quantum mechanical states. If the molecule possesses symmetries, it will belong to a point group, and the normal modes will "transform as" an irreducible representation under that group. The normal modes can then be qualitatively determined by applying group theory and projecting the irreducible representation onto the cartesian coordinates. For example, when this treatment is applied to CO_2 , it is found that the C=O stretches are not independent, but rather there is a O=C=O symmetric stretch and an O=C=O asymmetric stretch.

- symmetric stretching: the sum of the two C-O stretching coordinates; the two C-O bond lengths change by the same amount and the carbon atom is stationary. $Q = q_1 + q_2$
- asymmetric stretching: the difference of the two C-O stretching coordinates; one C-O bond length increases while the other decreases. $Q = q_1 - q_2$

When two or more normal coordinates belong to the same irreducible representation of the molecular point group (colloquially, have the same symmetry) there is "mixing" and the coefficients of the combination cannot be determined *a priori*. For example, in the linear molecule hydrogen cyanide, HCN, The two stretching vibrations are

1. principally C-H stretching with a little C-N stretching; $Q_1 = q_1 + a q_2$ ($a \ll 1$)
2. principally C-N stretching with a little C-H stretching; $Q_2 = b q_1 + q_2$ ($b \ll 1$)

The coefficients a and b are found by performing a full normal coordinate analysis by means of the Wilson GF method.^[4]

Newtonian mechanics

Perhaps surprisingly, molecular vibrations can be treated using Newtonian mechanics to calculate the correct vibration frequencies. The basic assumption is that each vibration can be treated as though it corresponds to a spring. In the harmonic approximation the spring obeys Hooke's law: the force required to extend the spring is proportional to the extension. The proportionality constant is known as a *force constant*, k . The anharmonic oscillator is considered elsewhere.^[5]

$$\text{Force} = -kQ$$

By Newton's second law of motion this force is also equal to a "mass", m , times acceleration.

$$\text{Force} = m \frac{d^2Q}{dt^2}$$

Since this is one and the same force the ordinary differential equation follows.

$$m \frac{d^2Q}{dt^2} + kQ = 0$$

The solution to this equation of simple harmonic motion is

$$Q(t) = A \cos(2\pi\nu t); \quad \nu = \frac{1}{2\pi} \sqrt{\frac{k}{m}}.$$

A is the maximum amplitude of the vibration coordinate Q . It remains to define the "mass", m . In a homonuclear diatomic molecule such as N_2 , it is half the mass of one atom. In a heteronuclear diatomic molecule, AB, it is the reduced mass, μ given by

$$\frac{1}{\mu} = \frac{1}{m_A} + \frac{1}{m_B}.$$

The use of the reduced mass ensures that the centre of mass of the molecule is not affected by the vibration. In the harmonic approximation the potential energy of the molecule is a quadratic function of the normal coordinate. It follows that the force-constant is equal to the second derivative of the potential energy.

$$k = \frac{\partial^2 V}{\partial Q^2}$$

When two or more normal vibrations have the same symmetry a full normal coordinate analysis must be performed (see GF method). The vibration frequencies, ν_i are obtained from the eigenvalues, λ_i , of the matrix product $\mathbf{GF}$. $\mathbf{G}$ is a matrix of numbers derived from the masses of the atoms and the geometry of the molecule.^[4] $\mathbf{F}$ is a matrix derived from force-constant values. Details concerning the determination of the eigenvalues can be found in ^[6].

Quantum mechanics

In the harmonic approximation the potential energy is a quadratic function of the normal coordinates. Solving the Schrödinger wave equation, the energy states for each normal coordinate are given by

$$E_n = \left(n + \frac{1}{2}\right) h \frac{1}{2\pi} \sqrt{\frac{k}{m}},$$

where n is a quantum number that can take values of 0, 1, 2 ... The difference in energy when n changes by 1 are therefore equal to the energy derived using classical mechanics. See quantum harmonic oscillator for graphs of the first 5 wave functions. Knowing the wave functions, certain selection rules can be formulated. For example, for a harmonic oscillator transitions are allowed only when the quantum number n changes by one,

$$\Delta n = \pm 1$$

but this does not apply to an anharmonic oscillator; the observation of overtones is only possible because vibrations are anharmonic. Another consequence of anharmonicity is that transitions such as between states $n=2$ and $n=1$ have slightly less energy than transitions between the ground state and first excited state. Such a transition gives rise to a hot band.

Intensities

In an infrared spectrum the intensity of an absorption band is proportional to the derivative of the molecular dipole moment with respect to the normal coordinate.^[7] The intensity of Raman bands depends on polarizability.

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Further reading

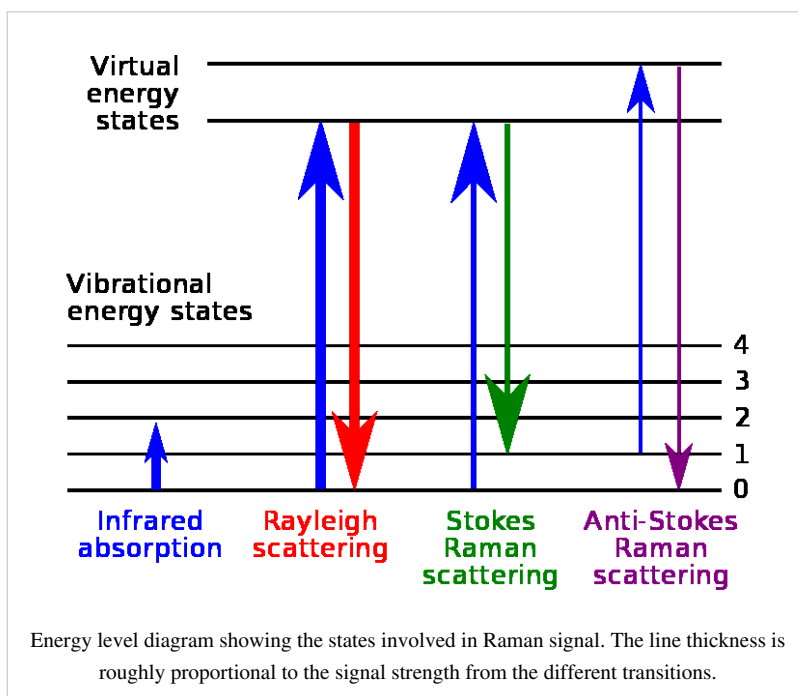
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External links

- Free Molecular Vibration code developed by Zs. Szabó and R. Scipioni (http://www.evtsz.bme.hu/web/staff/szabo/web_molecular_vibration/molec_vib_code.html)
- Molecular vibration and absorption (<http://www.lsbu.ac.uk/water/vibrat.html>)
- small explanation of vibrational spectra and a table including force constants (<http://hyperphysics.phy-astr.gsu.edu/Hbase/molecule/vibspe.html>).
- Character tables for chemically important point groups (<http://symmetry.jacobs-university.de/>)

Raman spectroscopy

Raman spectroscopy (named after C. V. Raman, pronounced /'rɑ:mən/) is a spectroscopic technique used to study vibrational, rotational, and other low-frequency modes in a system.^[1] It relies on inelastic scattering, or Raman scattering, of monochromatic light, usually from a laser in the visible, near infrared, or near ultraviolet range. The laser light interacts with molecular vibrations, phonons or other excitations in the system, resulting in the energy of the laser photons being shifted up or down. The shift in energy gives information about the phonon modes in the system. Infrared spectroscopy yields similar, but complementary, information.



Typically, a sample is illuminated with a laser beam. Light from the illuminated spot is collected with a lens and sent through a monochromator. Wavelengths close to the laser line, due to elastic Rayleigh scattering, are filtered out while the rest of the collected light is dispersed onto a detector.

Spontaneous Raman scattering is typically very weak, and as a result the main difficulty of Raman spectroscopy is separating the weak inelastically scattered light from the intense Rayleigh scattered laser light. Historically, Raman spectrometers used holographic gratings and multiple dispersion stages to achieve a high degree of laser rejection. In the past, photomultipliers were the detectors of choice for dispersive Raman setups, which resulted in long acquisition times. However, modern instrumentation almost universally employs notch or edge filters for laser rejection and spectrographs (either axial transmissive (AT), Czerny-Turner (CT) monochromator) or FT (Fourier transform spectroscopy based), and CCD detectors.

There are a number of advanced types of Raman spectroscopy, including surface-enhanced Raman, resonance Raman, tip-enhanced Raman, polarised Raman, stimulated Raman (analogous to stimulated emission), transmission Raman, spatially-offset Raman, and hyper Raman.

Basic theory

The Raman effect occurs when light impinges upon a molecule and interacts with the electron cloud and the bonds of that molecule. For the spontaneous Raman effect, which is a form of scattering, a photon excites the molecule from the ground state to a virtual energy state. When the molecule relaxes it emits a photon and it returns to a different rotational or vibrational state. The difference in energy between the original state and this new state leads to a shift in the emitted photon's frequency away from the excitation wavelength. The Raman effect, which is a light scattering phenomenon, should not be confused with absorption (as with fluorescence) where the molecule is excited to a discrete (not virtual) energy level.

If the final vibrational state of the molecule is more energetic than the initial state, then the emitted photon will be shifted to a lower frequency in order for the total energy of the system to remain balanced. This shift in frequency is designated as a Stokes shift. If the final vibrational state is less energetic than the initial state, then the emitted photon will be shifted to a higher frequency, and this is designated as an Anti-Stokes shift. Raman scattering is an example of inelastic scattering because of the energy transfer between the photons and the molecules during their interaction.

A change in the molecular polarization potential — or amount of deformation of the electron cloud — with respect to the vibrational coordinate is required for a molecule to exhibit a Raman effect. The amount of the polarizability change will determine the Raman scattering intensity. The pattern of shifted frequencies is determined by the rotational and vibrational states of the sample.

History

Although the inelastic scattering of light was predicted by Adolf Smekal in 1923, it is not until 1928 that it was observed in practice. The Raman effect was named after one of its discoverers, the Indian scientist Sir C. V. Raman who observed the effect by means of sunlight (1928, together with K. S. Krishnan and independently by Grigory Landsberg and Leonid Mandelstam).^[1] Raman won the Nobel Prize in Physics in 1930 for this discovery accomplished using sunlight, a narrow band photographic filter to create monochromatic light and a "crossed" filter to block this monochromatic light. He found that light of changed frequency passed through the "crossed" filter.

Systematic pioneering theory of the Raman effect was developed by Czechoslovak physicist George Placzek between 1930 and 1934.^[2] The mercury arc became the principal light source, first with photographic detection and then with spectrophotometric detection. At the present time, lasers are used as light sources.

Raman spectra

Raman spectra are typically expressed in wavenumbers, which have units of inverse length. In order to convert between spectral wavelength and wavenumbers of shift in the Raman spectrum, the following formula can be used:

$$\Delta w = \left(\frac{1}{\lambda_0} - \frac{1}{\lambda_1} \right),$$

where Δw is the Raman shift expressed in wavenumber, λ_0 is the excitation wavelength, and λ_1 is the Raman spectrum wavelength. Most commonly, the units chosen for expressing wavenumber in Raman spectra is inverse centimeters (cm^{-1}). Since wavelength is often expressed in units of nanometers (nm), the formula above can scale for this units conversion explicitly, giving

$$\Delta w(\text{cm}^{-1}) = \left(\frac{1}{\lambda_0(\text{nm})} - \frac{1}{\lambda_1(\text{nm})} \right) \times 10^7 \frac{(\text{nm})}{(\text{cm})},$$

Applications

Raman spectroscopy is commonly used in chemistry, since vibrational information is specific to the chemical bonds and symmetry of molecules. Therefore, it provides a fingerprint by which the molecule can be identified. For instance, the vibrational frequencies of SiO , Si_2O_2 , and Si_3O_3 were identified and assigned on the basis of normal coordinate analyses using infrared and Raman spectra.^[3] The fingerprint region of organic molecules is in the (wavenumber) range $500\text{--}2000\text{ cm}^{-1}$. Another way that the technique is used to study changes in chemical bonding, e.g., when a substrate is added to an enzyme.

Raman gas analyzers have many practical applications. For instance, they are used in medicine for real-time monitoring of anaesthetic and respiratory gas mixtures during surgery.

In solid state physics, spontaneous Raman spectroscopy is used to, among other things, characterize materials, measure temperature, and find the crystallographic orientation of a sample. As with single molecules, a given solid material has characteristic phonon modes that can help an experimenter identify it. In addition, Raman spectroscopy can be used to observe other low frequency excitations of the solid, such as plasmons, magnons, and superconducting gap excitations. The spontaneous Raman signal gives information on the population of a given phonon mode in the ratio between the Stokes (downshifted) intensity and anti-Stokes (upshifted) intensity.

Raman scattering by an anisotropic crystal gives information on the crystal orientation. The polarization of the Raman scattered light with respect to the crystal and the polarization of the laser light can be used to find the orientation of the crystal, if the crystal structure (to be specific, its point group) is known.

Raman active fibers, such as aramid and carbon, have vibrational modes that show a shift in Raman frequency with applied stress. Polypropylene fibers also exhibit similar shifts. The radial breathing mode is a commonly used technique to evaluate the diameter of carbon nanotubes. In nanotechnology, a Raman microscope can be used to analyze nanowires to better understand the composition of the structures.

Spatially-offset Raman spectroscopy (SORS), which is less sensitive to surface layers than conventional Raman, can be used to discover counterfeit drugs without opening their internal packaging, and for non-invasive monitoring of biological tissue.^[4] Raman spectroscopy can be used to investigate the chemical composition of historical documents such as the Book of Kells and contribute to knowledge of the social and economic conditions at the time the documents were produced.^[5] This is especially helpful because Raman spectroscopy offers a non-invasive way to determine the best course of preservation or conservation treatment for such materials.

Raman spectroscopy is being investigated as a means to detect explosives for airport security.^[6]

Raman spectroscopy has also been used to confirm the prediction of existence of low-frequency phonons^[7] in proteins and DNA (see, e.g.,^{[8] [9] [10] [11]} greatly stimulating the studies of low-frequency collective motion in proteins and DNA and their biological functions.^{[12] [13]}

Microspectroscopy

Raman spectroscopy offers several advantages for microscopic analysis. Since it is a scattering technique, specimens do not need to be fixed or sectioned. Raman spectra can be collected from a very small volume ($< 1\text{ }\mu\text{m}$ in diameter); these spectra allow the identification of species present in that volume. Water does not generally interfere with Raman spectral analysis. Thus, Raman spectroscopy is suitable for the microscopic examination of minerals, materials such as polymers and ceramics, cells and proteins. A Raman microscope begins with a standard optical microscope, and adds an excitation laser, a monochromator, and a sensitive detector (such as a charge-coupled device (CCD), or photomultiplier tube (PMT)). FT-Raman has also been used with microscopes.

In *direct imaging*, the whole field of view is examined for scattering over a small range of wavenumbers (Raman shifts). For instance, a wavenumber characteristic for cholesterol could be used to record the distribution of cholesterol within a cell culture.

The other approach is *hyperspectral imaging* or *chemical imaging*, in which thousands of Raman spectra are acquired from all over the field of view. The data can then be used to generate images showing the location and amount of different components. Taking the cell culture example, a hyperspectral image could show the distribution of cholesterol, as well as proteins, nucleic acids, and fatty acids. Sophisticated signal- and image-processing techniques can be used to ignore the presence of water, culture media, buffers, and other interferents.

Raman microscopy, and in particular confocal microscopy, has very high spatial resolution. For example, the lateral and depth resolutions were 250 nm and 1.7 μm , respectively, using a confocal Raman microspectrometer with the 632.8 nm line from a Helium-Neon laser with a pinhole of 100 μm diameter. Since the objective lenses of microscopes focus the laser beam to several micrometres in diameter, the resulting photon flux is much higher than achieved in conventional Raman setups. This has the added benefit of enhanced fluorescence quenching. However, the high photon flux can also cause sample degradation, and for this reason some setups require a thermally conducting substrate (which acts as a heat sink) in order to mitigate this process.

By using Raman microspectroscopy, *in vivo* time- and space-resolved Raman spectra of microscopic regions of samples can be measured. As a result, the fluorescence of water, media, and buffers can be removed. Consequently *in vivo* time- and space-resolved Raman spectroscopy is suitable to examine proteins, cells and organs.

Raman microscopy for biological and medical specimens generally uses near-infrared (NIR) lasers (785 nm diodes and 1064 nm Nd:YAG are especially common). This reduces the risk of damaging the specimen by applying higher energy wavelengths. However, the intensity of NIR Raman is low (owing to the ω^4 dependence of Raman scattering intensity), and most detectors required very long collection times. Recently, more sensitive detectors have become available, making the technique better suited to general use. Raman microscopy of inorganic specimens, such as rocks and ceramics and polymers, can use a broader range of excitation wavelengths.^[14]

Polarized analysis

The polarization of the Raman scattered light also contains useful information. This property can be measured using (plane) polarized laser excitation and a polarization analyzer. Spectra acquired with the analyzer set at both perpendicular and parallel to the excitation plane can be used to calculate the depolarization ratio. Study of the technique is useful in teaching the connections between group theory, symmetry, Raman activity, and peaks in the corresponding Raman spectra.

The spectral information arising from this analysis gives insight into molecular orientation and vibrational symmetry. In essence, it allows the user to obtain valuable information relating to the molecular shape, for example in synthetic chemistry or polymorph analysis. It is often used to understand macromolecular orientation in crystal lattices, liquid crystals or polymer samples.^[15]

Variations

Several variations of Raman spectroscopy have been developed. The usual purpose is to enhance the sensitivity (e.g., surface-enhanced Raman), to improve the spatial resolution (Raman microscopy), or to acquire very specific information (resonance Raman).

- **Surface Enhanced Raman Spectroscopy (SERS)** - Normally done in a silver or gold colloid or a substrate containing silver or gold. Surface plasmons of silver and gold are excited by the laser, resulting in an increase in the electric fields surrounding the metal. Given that Raman intensities are proportional to the electric field, there is large increase in the measured signal (by up to 10^{11}). This effect was originally observed by Martin Fleischmann but the prevailing explanation was proposed by Van Duyne in 1977.^[16] A comprehensive theory of the effect is that given by Lombardi and Birke in 2008 called the a Unified Approach to Surface-Enhanced Raman Spectroscopy.^[17]

- **Resonance Raman spectroscopy** - The excitation wavelength is matched to an electronic transition of the molecule or crystal, so that vibrational modes associated with the excited electronic state are greatly enhanced. This is useful for studying large molecules such as polypeptides, which might show hundreds of bands in "conventional" Raman spectra. It is also useful for associating normal modes with their observed frequency shifts.^[18]
- **Surface-Enhanced Resonance Raman Spectroscopy (SERRS)** - A combination of SERS and resonance Raman spectroscopy that uses proximity to a surface to increase Raman intensity, and excitation wavelength matched to the maximum absorbance of the molecule being analysed.
- **Hyper Raman** - A non-linear effect in which the vibrational modes interact with the second harmonic of the excitation beam. This requires very high power, but allows the observation of vibrational modes that are normally "silent". It frequently relies on SERS-type enhancement to boost the sensitivity.^[19]
- **Spontaneous Raman Spectroscopy (SRS)** - Used to study the temperature dependence of the Raman spectra of molecules.
- **Optical Tweezers Raman Spectroscopy (OTRS)** - Used to study individual particles, and even biochemical processes in single cells trapped by optical tweezers.
- **Stimulated Raman Spectroscopy** - A spatially coincident, two color pulse (with polarization either parallel or perpendicular) transfers the population from ground to a rovibrationally excited state, if the difference in energy corresponds to an allowed Raman transition, and if neither frequency corresponds to an electronic resonance. Two photon UV ionization, applied after the population transfer but before relaxation, allows the intra-molecular or inter-molecular Raman spectrum of a gas or molecular cluster (indeed, a given conformation of molecular cluster) to be collected. This is a useful molecular dynamics technique.
- **Spatially Offset Raman Spectroscopy (SORS)** - The Raman scatter is collected from regions laterally offset away from the excitation laser spot, leading to significantly lower contributions from the surface layer than with traditional Raman spectroscopy.^[20]
- **Coherent anti-Stokes Raman spectroscopy (CARS)** - Two laser beams are used to generate a coherent anti-Stokes frequency beam, which can be enhanced by resonance.
- **Raman optical activity (ROA)** - Measures vibrational optical activity by means of a small difference in the intensity of Raman scattering from chiral molecules in right- and left-circularly polarized incident light or, equivalently, a small circularly polarized component in the scattered light.^[21]
- **Transmission Raman** - Allows probing of a significant bulk of a turbid material, such as powders, capsules, living tissue, etc. It was largely ignored following investigations in the late 1960s^[22] but was rediscovered in 2006 as a means of rapid assay of pharmaceutical dosage forms.^[23] There are also medical diagnostic applications.^[24]
- **Inverse Raman spectroscopy.**
- **Tip-Enhanced Raman Spectroscopy (TERS)** - Uses a metallic (usually silver-/gold-coated AFM or STM) tip to enhance the Raman signals of molecules situated in its vicinity. The spatial resolution is approximately the size of the tip apex (20-30 nm). TERS has been shown to have sensitivity down to the single molecule level.

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External links

- Raman FAQs (frequently asked questions) (<http://www.horiba.com/scientific/products/raman-spectroscopy/tutorial-faqs/raman-faqs/>), horiba.com
- Raman on SiGe Superlattice (http://content.piacon.com/Uploads/Princeton/Documents/Library/UpdatedLibrary/Raman_on_SiGe_Superlattice_Using_TriVista.pdf), princetoninstruments.com
- An introduction to Raman spectroscopy (<http://www.horiba.com/scientific/products/raman-spectroscopy/raman-resource/raman-tutorial/>), horiba.com
- Raman Application examples (<http://www.horiba.com/scientific/products/raman-spectroscopy/application-notes/>), horiba.com
- An introduction on Raman Scattering (<http://www.d3technologies.co.uk/en/10371.aspx>), d3technologies.co.uk

- Raman Spectroscopy Applications (<http://www.renishaw.com/en/raman-spectroscopy-applications--6259>), renishaw.com
 - Raman Data Search and Storage (<http://ramandata.sourceforge.net>) - The free application with a wonderful database of Raman data (vibrations, assignment) with storage function and Raman spectra (discussions) with search function. ramandata.sourceforge.net
 - Romanian Database of Raman Spectroscopy (<http://rdrs.uaic.ro>) - This database contains mineral species (natural and synthetic) with description of crystal structure, sample image, number of sample, origin, Raman spectrum and vibrations, Raman discussion and references. Also, this site contains artefacts sample with sample image and pigment spectrum; black, red, white or blue pigment. rdrs.uaic.ro
 - Chemical Imaging Without Dyeing (<http://witec.de/en/download/Raman/ImagingMicroscopy04.pdf>), witec.de
 - DoITPoMS Teaching and Learning Package - Raman Spectroscopy (<http://www.doitpoms.ac.uk/tlplib/raman/index.php>) - an introduction, aimed at undergraduate level. doitpoms.ac.uk
 - Raman Spectroscopy Tutorial (http://161.58.205.25/Raman_Spectroscopy/rtr-ramantutorial.php?ss=800) - A detailed explanation of Raman Spectroscopy including Resonance-Enhanced Raman Scattering and Surface-Enhanced Raman Scattering. 161.25.205.25
 - The Science Show, ABC Radio National (<http://www.abc.net.au/rn/science/ss/stories/s1581469.htm>) - Interview with Scientist on NASA funded project to build Raman Spectrometer for the 2009 Mars mission: a cellular phone size device to detect almost any substance known, with commercial <USD\$5000 commercial spin-off, prototyped by June 2006. abc.net.au/rn
 - Raman spectroscopy for medical diagnosis (http://pubs.acs.org/subscribe/journals/ancham/79/i11/pdf/0607feature_griffiths.pdf) from the June 1, 2007 issue of *Analytical Chemistry* (<http://pubs3.acs.org/acs/journals/toc.page?incoden=ancham&indecade=0&involume=79&inissue=11>), pubs.acs.org
 - Spontaneous Raman Scattering (SRS) (<http://www.lavision.de/en/techniques/raman-scattering.php>), lavision.de
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Coherent anti-Stokes Raman spectroscopy

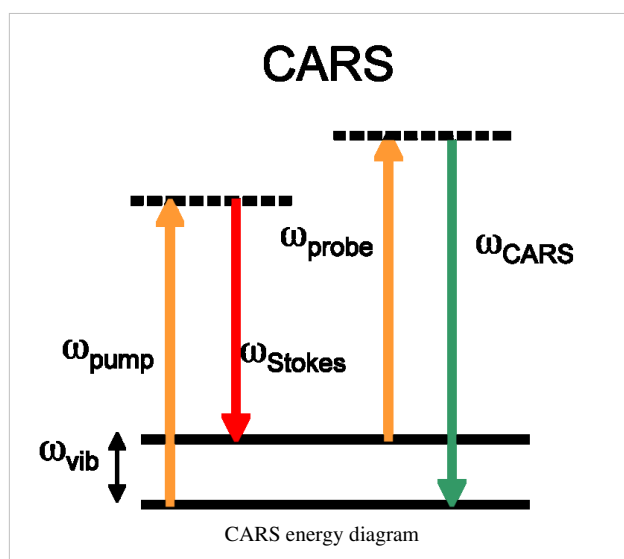
Coherent anti-Stokes Raman spectroscopy, also called Coherent anti-Stokes Raman scattering spectroscopy (CARS), is a form of spectroscopy used primarily in chemistry, physics and related fields. It is sensitive to the same vibrational signatures of molecules as seen in Raman spectroscopy, typically the nuclear vibrations of chemical bonds. Unlike Raman spectroscopy, CARS employs multiple photons to address the molecular vibrations, and produces a signal in which the emitted waves are coherent with one another. As a result, CARS is orders of magnitude stronger than spontaneous Raman emission. CARS is a third-order nonlinear optical process involving three laser beams: a pump beam of frequency ω_p , a Stokes beam of frequency ω_s and a probe beam at frequency ω_{pr} . These beams interact with the sample and generate a coherent optical signal at the anti-Stokes frequency ($\omega_p - \omega_s + \omega_{pr}$). The latter is resonantly enhanced when the frequency difference between the pump and the Stokes beams ($\omega_p - \omega_s$) coincides with the frequency of a Raman resonance, which is the basis of the technique's intrinsic vibrational contrast mechanism.^{[1] [2]}

History

The acronym CARS, which invokes a seemingly inadvertent relation to automobiles, is actually closely related to the birth story of the technique. In 1965, a paper was published by two researchers of the Scientific Laboratory at the Ford Motor Company, P. D. Maker and R. W. Terhune, in which the CARS phenomenon was reported for the first time.^[3] Maker and Terhune used a pulsed ruby laser to investigate the third order response of several materials. They first passed the ruby beam of frequency ω through a Raman shifter to create a second beam at $\omega - \omega_v$, and then directed the two beams simultaneously onto the sample. When the pulses from both beams overlapped in space and time, the Ford researchers observed a signal at $\omega + \omega_v$, which is the blue-shifted CARS signal. They also demonstrated that the signal increases significantly when the difference frequency ω_v between the incident beams matches a Raman frequency of sample. Maker and Terhune called their technique simply 'three wave mixing experiments'. The name coherent anti-Stokes Raman spectroscopy was assigned almost ten years later, by Begley et al. at Stanford University in 1974.^[4] Since then, this vibrationally sensitive nonlinear optical technique is commonly known as CARS.

Principle

The CARS process can be physically explained by using either a classical oscillator model or by using a quantum mechanical model that incorporates the energy levels of the molecule. Classically, the Raman active vibrator is modeled as a (damped) harmonic oscillator with a characteristic frequency of ω_v . In CARS, this oscillator is not driven by a single optical wave, but by the difference frequency ($\omega_p - \omega_s$) between the pump and the Stokes beams instead. This driving mechanism is similar to hearing the low combination tone when striking two different high tone piano keys: your ear is sensitive to the difference frequency of the high tones. Similarly, the Raman oscillator is susceptible to the difference frequency of two optical



waves. When the difference frequency $\omega_p - \omega_S$ approaches ω_v , the oscillator is driven very efficiently. On a molecular level, this implies that the electron cloud surrounding the chemical bond is vigorously oscillating with the frequency $\omega_p - \omega_S$. These electron motions alter the optical properties of the sample, i.e. there is a periodic modulation of the refractive index of the material. This periodic modulation can be probed by a third laser beam, the probe beam. When the probe beam is propagating through the periodically altered medium, it acquires the same modulation. Part of the probe, originally at ω_{pr} will now get modified to $\omega_{pr} + \omega_p - \omega_S$, which is the observed anti-Stokes emission. Under certain beam geometries, the anti-Stokes emission may diffract away from the probe beam, and can be detected in a separate direction.

While intuitive, this classical picture does not take into account the quantum mechanical energy levels of the molecule. Quantum mechanically, the CARS process can be understood as follows. Our molecule is initially in the ground state, the lowest energy state of the molecule. The pump beam excites the molecule to a virtual state. A virtual state is not an eigenstate of the molecule and it can not be occupied but it does allow for transitions between otherwise uncoupled real states. If a Stokes beam is simultaneously present along with the pump, the virtual state can be used as an instantaneous gateway to address a vibrational eigenstate of the molecule. The joint action of the pump and the Stokes has effectively established a coupling between the ground state and the vibrationally excited state of the molecule. The molecule is now in two states at the same time: it resides in a coherent superposition of states. This coherence between the states can be probed by the probe beam, which promotes the system to a virtual state. Again, the molecule cannot stay in the virtual state and will fall back instantaneously to the ground state under the emission of a photon at the anti-Stokes frequency. The molecule is no longer in a superposition, as it resides again in one state, the ground state. In the quantum mechanical model, no energy is deposited in the molecule during the CARS process. Instead, the molecule acts like a medium for converting the frequencies of the three incoming waves into a CARS signal (a parametric process). There are, however, related coherent Raman process that occur simultaneously which do deposit energy into the molecule.

Comparison to Raman spectroscopy

CARS is often compared to Raman spectroscopy as both techniques probe the same Raman active modes. Raman can be done using a single continuous wave (CW) laser whereas CARS requires (generally) two pulsed laser sources. The Raman signal is detected on the red side of the incoming radiation where it might have to compete with other fluorescent processes. The CARS signal is detected on the blue side, which is free from fluorescence, but it comes with a non-resonant contribution. The differences between the signals from Raman and CARS (there are many variants of both techniques) stems largely from the fact that Raman relies on a spontaneous transition whereas CARS relies on a coherently driven transition. The total Raman signal collected from a sample is the incoherent addition of the signal from individual molecules. It is therefore linear in the concentration of those molecules and the signal is emitted in all directions. The total CARS signal comes from a coherent addition of the signal from individual molecules. For the coherent addition to be additive, phase-matching must be fulfilled. For tight focusing conditions this is generally not a restriction. Once phase-matching is fulfilled the signal amplitude grows linear with distance so that the power grows quadratically. This signal forms a collimated beam that is therefore easily collected. The fact that the CARS signal is quadratic in the distance makes it quadratic with respect to the concentration and therefore especially sensitive to the majority constituent. The total CARS signal also contains an inherent non-resonant background. This non-resonant signal can be considered as the result of (several) far off-resonance transitions that also add coherently. The resonant amplitude contains a phase shift of π over the resonance whereas the non-resonant part does not. The spectral line shape of the CARS intensity therefore resembles a Fano-profile which is shifted with respect to the Raman signal. To compare the spectra from multi-component compounds, the (resonant) CARS spectral amplitude should be compared to the Raman spectral intensity.

Theoretically Raman spectroscopy and CARS spectroscopy are equally sensitive as they use the same molecular transitions. However, given the limits on input power (damage threshold) and detector noise (integration time), the

signal from a single transition can be collected much faster in practical situation (a factor of 10^5) using CARS. Imaging of known substances (known spectra) is therefore often done using CARS. Given the fact that CARS is a higher order nonlinear process, the CARS signal from a single molecule is larger than the Raman signal from a single molecule for a sufficiently high driving intensity. However at very low concentrations, the advantages of the coherent addition for CARS signal reduces and the presence of the incoherent background becomes an increasing problem.

Since CARS is such a nonlinear process there are not really any 'typical' experimental numbers. One example is given below under the explicit warning that just changing the pulse duration by one order of magnitude changes the CARS signal by three orders of magnitude. The comparison should only be used as an indication of the order of magnitude of the signals. 200 mW average power input (CW for the Raman), in a 0.9NA objective with a center wavelength around 800 nm, constitutes a power density of 26 MW/cm^2 (focal length = 1.5 micrometre, focal volume = $1.16 \text{ micrometre}^3$, photon energy = $2.31 \cdot 10^{-19} \text{ J}$ or 1.44 eV). The Raman cross section for the vibration of the aromatic ring in Toluene around 1000 cm^{-1} is on the order of $10^{-29} \text{ cm}^2/\text{molecule} \cdot \text{steradian}$. Therefore the Raman signal is around $26 \cdot 10^{-22} \text{ W/molecule} \cdot \text{steradian}$ or $3.3 \cdot 10^{-21} \text{ W/molecule}$ (over 4π). That is 0.014 photon/sec*molecule. The density of Toluene = $0.8668 \cdot 10^3 \text{ kg/m}^3$, Molecular mass = $92.14 \cdot 10^{-3} \text{ kg/mol}$. Therefore the focal volume (~ 1 cubic micrometre) contains $6 \cdot 10^9$ molecules. Those molecules together generate a Raman signal in the order of $2 \cdot 10^{-11} \text{ W}$ (20pW) or roughly one hundred million photons/sec (over a 4π solid angle). A CARS experiment with similar parameters (150 mW at 1064 nm, 200 mW at 803.5 nm, 15ps pulses at 80Mhz repetition frequency, same objective lens) yields roughly $17.5 \cdot 10^{-6} \text{ W}$ (on the 3000 cm^{-1} line, which has 1/3 of the strength and roughly 3 times the width). This CARS power is roughly 10^6 higher than the Raman but since there are $6 \cdot 10^9$ molecules, the signal per molecule from CARS is only $4 \cdot 10^{-25} \text{ W/molecule} \cdot \text{sec}$ or $1.7 \cdot 10^{-6}$ photons/molecule*sec. If we allow for two factors of three (line strength and line width) than the spontaneous Raman signal per molecule still exceeds the CARS per molecule by a more than two orders of magnitude. The coherent addition of the CARS signal from the molecules however yields a total signal that is much higher than the Raman.

The sensitivity in many CARS experiments is not limited by the detection of CARS photons but rather by the distinction between the resonant and non-resonant part of the CARS signal.

Applications

CARS is used for species selective microscopy and combustion diagnostics. The first exploits the selectivity of vibrational spectroscopy whereas the latter is aimed at temperature measurements; the CARS signal is temperature dependent. The strength of the signal scales (non-linearly) with the difference in the ground state population and the vibrationally excited state population. Since the population of states follows the temperature dependent Boltzmann Distribution, the CARS signal carries an intrinsic temperature dependence as well. This temperature dependence makes CARS a popular technique for monitoring the temperature of hot gases and flames.

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Further reading

- C.L. Evans and X.S. Xie. 2008. Coherent Anti-Stokes Raman Scattering Microscopy: Chemical Imaging for Biology and Medicine., doi:10.1146/annurev.anchem.1.031207.112754 *Annual Review of Analytical Chemistry*, 1: 883-909.

Time-resolved spectroscopy

In physics and physical chemistry, **time-resolved spectroscopy** is the study of dynamic processes in materials or chemical compounds by means of spectroscopic techniques. Most often, processes are studied that occur after illumination of a material, but in principle, the technique can be applied to any process that leads to a change in properties of a material. With the help of pulsed lasers, it is possible to study processes that occur on time scales as short as 10^{-14} seconds. The rest of the article discusses different types of time-resolved spectroscopy.

Transient-absorption spectroscopy

Transient-absorption spectroscopy is an extension of absorption spectroscopy. Here, the absorbance at a particular wavelength or range of wavelengths of a sample is measured as a function of time after excitation by a flash of light. In a typical experiment, both the light for excitation ('pump') and the light for measuring the absorbance ('probe') are generated by a pulsed laser. If the process under study is slow, then the time resolution can be obtained with a continuous (i.e., not pulsed) probe beam and repeated conventional spectrophotometric techniques.

Examples of processes that can be studied:

- Optical gain spectroscopy of semiconductor laser materials.
- Chemical reactions that are initiated by light (or 'photoinduced chemical reactions');
- The transfer of excitation energy between molecules, parts of molecules, or molecules and their environment;
- The behaviour of electrons that are freed from a molecule or crystalline material.

Other multiple-pulse techniques

Transient spectroscopy as discussed above is a technique that involves two pulses. There are many more techniques that employ two or more pulses, such as:

- Photon echoes.
- Four-wave mixing (involves three laser pulses)

The interpretation of experimental data from these techniques is usually much more complicated than in transient-absorption spectroscopy.

Nuclear magnetic resonance and electron spin resonance are often implemented with multiple-pulse techniques, though with radio waves and micro waves instead of visible light.

Time-resolved infrared spectroscopy

Time-resolved infrared (TRIR) spectroscopy also employs a two-pulse, "pump-probe" methodology. The pump pulse is typically in the UV region and is often generated by a high-powered Nd:YAG laser, whereas the probe beam is in the infrared region. This technique currently operates down to the picosecond time regime and surpasses transient absorption and emission spectroscopy by providing *structural* information on the excited-state kinetics of both dark and emissive states.

Time-resolved fluorescence spectroscopy

Time-resolved fluorescence spectroscopy is an extension of fluorescence spectroscopy. Here, the fluorescence of a sample is monitored as a function of time after excitation by a flash of light. The time resolution can be obtained in a number of ways, depending on the required sensitivity and time resolution:

- With fast-detection electronics (nanoseconds and slower)
- With a streak camera (picoseconds and slower)
- With optical gating (femtoseconds-nanoseconds) - a short laser pulse acts as a gate for the detection of fluorescence light; only fluorescence light that arrives at the detector at the same time as the gate pulse is detected. This technique has the best time resolution, but the efficiency is rather low. An extension of this optical gating technique is to use a "Kerr gate", which allows the scattered Raman signal to be collected before the (slower) fluorescence signal overwhelms it. This technique can greatly improve the signal:noise ratio of Raman spectra.

Terahertz spectroscopy

Terahertz frequency radiation for spectroscopy is typically generated in one of three ways:

- time domain terahertz spectroscopy (TDS), using ultrashort laser pulses
- photomixing, mixing two radiation sources to generate their difference frequency
- Fourier transform spectroscopy, using a blackbody radiation source

X-ray spectroscopy

X-ray spectroscopy is a gathering name for several spectroscopic techniques for determining the electronic structure of materials by using x-ray excitation.

X-ray emission spectroscopy

William Lawrence Bragg and William Henry Bragg, who were the 1914 Nobel Prize Winners, were the original pioneers in developing **X-ray emission spectroscopy** (also called X-ray fluorescence spectroscopy). He measured the X-ray wavelengths of many elements to high precision, using high-energy electrons as excitation source. He also painstakingly produced numerous diamond-ruled glass diffraction gratings for his spectrometers.

Intense and wavelength-tunable X-rays are now typically generated with synchrotrons. In a material, the X-rays may suffer an energy loss compared to the incoming beam. This energy loss of the re-emerging beam reflects an internal excitation of the atomic system, an X-ray analogue to the well-known Raman spectroscopy that is widely used in the optical region.

In the X-ray region there is sufficient energy to probe changes in the electronic state (transitions between orbitals; this is in contrast with the optical region, where the energy loss is often due to changes in the state of the rotational or vibrational degrees of freedom). For instance, in the ultra soft X-ray region (below about 1 keV), crystal field excitations give rise to the energy loss.

The photon-in-photon-out process may be thought of as a scattering event. When the x-ray energy corresponds to the binding energy of a core-level electron, this scattering process is resonantly enhanced by many orders of magnitude. This type of X-ray emission spectroscopy is often referred to as resonant inelastic X-ray scattering (RIXS).

Due to the wide separation of orbital energies of the core levels, it is possible to select a certain atom of interest. The small spatial extent of core level orbitals forces the RIXS process to reflect the electronic structure in close vicinity

of the chosen atom. Thus RIXS experiments give valuable information about the local electronic structure of complex systems, and theoretical calculations are relatively simple to perform.

Instrumentation

There exist several efficient designs for analyzing an X-ray emission spectrum in the ultra soft X-ray region. The figure of merit for such instruments is the spectral throughput, i.e. the product of detected intensity and spectral resolving power. Usually, it is possible to change the parameters within a certain range while keeping their product constant.

Grating spectrometers

Typically, the X-rays emerging from a sample must pass a source-defining slit, then optical elements (mirrors and/or gratings) disperse them by diffraction according to their wavelength and, finally, a detector is placed at their focal points.

Spherical grating mounts

Henry Augustus Rowland (1848–1901) devised an instrument that allowed the use of a single optical element that combines diffraction and focusing: a spherical grating. Reflectivity of X-rays is low regardless of the used material and therefore grazing incidence upon the grating is necessary. X-ray beams impinging on a smooth surface at a few degrees glancing angle of incidence undergo external total reflection which is taken advantage of to enhance the instrumental efficiency substantially.

Denote by R the radius of a spherical grating. Imagine a circle with half the radius R tangent to the center of the grating surface. This small circle is called the **Rowland circle**. If the entrance slit is anywhere on this circle, then a beam passing the slit and striking the grating will be split into a specularly reflected beam, and beams of all diffraction orders, that come into focus at certain points on the same circle.

Plane grating mounts

Similar to optical spectrometers, a plane grating spectrometer first needs optics that turns the divergent rays emitted by the x-ray source into a parallel beam. This may be achieved by using a parabolic mirror. The parallel rays emerging from this mirror strike a plane grating (with constant groove distance) at the same angle and are diffracted according to their wavelength. A second parabolic mirror then collects the diffracted rays at a certain angle and creates an image on a detector. A spectrum within a certain wavelength range can be recorded simultaneously by using a two-dimensional position-sensitive detector such as a microchannel photomultiplier plate or an X-ray sensitive CCD chip (film plates are also possible to use).

Interferometers

Instead of using the concept of multiple beam interference that gratings produce, the two rays may simply interfere. By recording the intensity of two such co-linearly at some fixed point and changing their relative phase one obtains an intensity spectrum as a function of path length difference. One can show that this is equivalent to a Fourier transformed spectrum as a function of frequency. The highest recordable frequency of such a spectrum is dependent on the minimum step size chosen in the scan and the frequency resolution (i.e. how well a certain wave can be defined in terms of its frequency) depends on the maximum path length difference achieved. The latter feature allows a much more compact design for achieving high resolution than for a grating spectrometer because x-ray wavelengths are small compared to attainable path length differences.

Other types of X-ray spectroscopy

- X-ray absorption spectroscopy
- X-ray magnetic circular dichroism

Electron spectroscopy

Electron spectroscopy is an analytical technique to study the electronic structure and its dynamics in atoms and molecules. In general an excitation source such as x-rays, electrons or synchrotron radiation will eject an electron from an inner-shell orbital of an atom. Detecting photoelectrons that are ejected by x-rays is called x-ray photoelectron spectroscopy (XPS) or electron spectroscopy for chemical analysis (ESCA). Detecting electrons that are ejected from higher orbitals to conserve energy during electron transitions is called Auger electron spectroscopy (AES).

Experimental applications include high-resolution measurements on the intensity and angular distributions of emitted electrons as well as on the total and partial ion yields. Ejected electrons can escape only from a depth of approximately 3 nanometers or less, making electron spectroscopy most useful to study surfaces of solid materials. Depth profiling is accomplished by combining an electron spectroscopy with a sputtering source that removes surface layers.

Synchrotron radiation research work has been carried out at the MAX Laboratory in Lund, Sweden, Elettra Storage Ring in Trieste, Italy, and at ALS in Berkeley, CA.

External links

- The University of Adelaide, Australia ^[1]
- The University of Oulu, Finland ^[2]

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Inelastic electron tunnelling spectroscopy

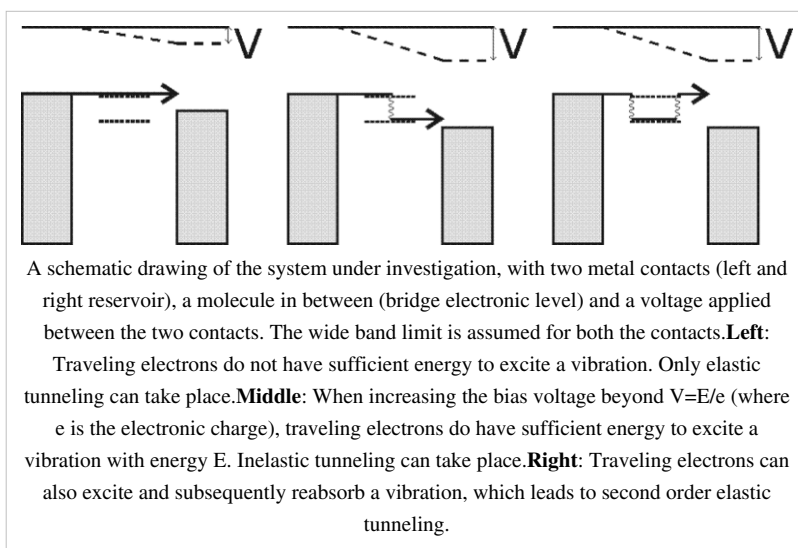
Inelastic electron tunneling spectroscopy (IETS) is an experimental tool for studying the vibrations of molecular adsorbates on metal oxides. It yields vibrational spectra of the adsorbates with high resolution (< 0.5 meV) and high sensitivity ($< 10^{13}$ molecules are required to provide a spectrum).^[1] An additional advantage is the fact that optically forbidden transitions may be observed as well.^[2] Within IETS, an oxide layer with molecules adsorbed on it is put between two metal plates.

A bias voltage is applied between the

two contacts. An energy diagram of the metal-oxide-metal device under bias is shown in the top figure. The metal contacts are characterized by a constant density of states, filled up to the Fermi energy. The metals are assumed to be equal. The adsorbates are situated on the oxide material. They are represented by a single bridge electronic level, which is the upper dashed line. If the insulator is thin enough, there is a finite probability that the incident electron tunnels through the barrier. Since the energy of the electron is not changed by this process, it is an elastic process. This is shown in the right figure.

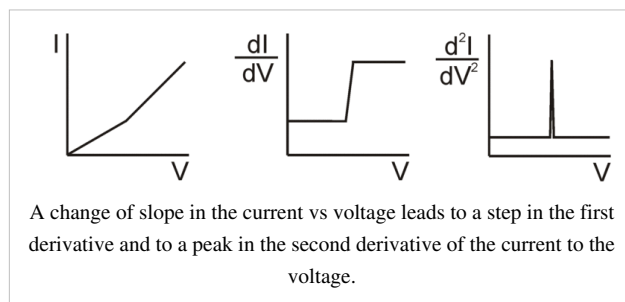
Some of the tunneling electrons can lose energy by exciting vibrations of the oxide or the adsorbate. These inelastic processes lead to a second tunneling path, which gives an additional current contribution to the tunneling current. Since the incident electron should have enough energy to excite this vibration, there is a minimum energy that is the onset of this (inelastic) process. This is shown in the middle figure, where the lower dashed line is a vibronic state. This minimum energy for the electron corresponds with a minimum bias voltage, which is the onset for the additional contribution. The inelastic contribution to the current is small compared to the elastic tunneling current ($\sim 0.1\%$) and is more clearly seen as a peak in the second derivative of the current to the bias voltage, as can be seen in the bottom figure.

There is however also an important correction to the elastic component of the tunneling current at the onset. This is a second order effect in electron-vibration coupling, where a vibration is emitted and reabsorbed or vice versa. This is shown in the upper figure on the right. Depending on the energetic parameters of the system, this correction may be negative and it may outweigh the positive contribution of the inelastic current, resulting in a dip in the IETS spectrum. This is experimentally verified in both regular IETS^[3] and in STM-IETS^[4] and is also predicted theoretically.^[5] Not only peaks and dips may be observed, but depending on the energetic parameters also derivative-like features may be observed, both experimentally^[6] and theoretically.^[7]



STM-IETS

Keeping the tip of a scanning tunneling microscope (STM) at fixed position over the surface and sweeping the bias voltage, one can record a I - V characteristic. This technique is called scanning tunneling spectroscopy (STS). The first derivative gives information about the local density of states (LDOS) of the substrate, assuming that the tip has a constant density of states. The second derivative gives information on vibrations of the adsorbate, exactly as in IETS. That is why this technique is commonly called STM-IETS. The role of the insulating oxide layer is played by the gap between the tip and the adsorbate.

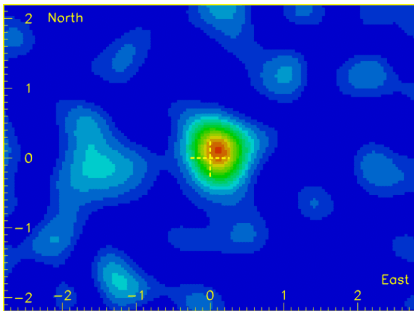


Nowadays molecular transport junctions have been produced with one single molecule between two electrodes, possibly with an additional, gate electrode near the molecule.^{[8] [9] [10]} The advantage of this method in comparison with STM-IETS is that there is contact between both electrodes and the adsorbate, whereas in STM-IETS there is always a tunneling gap between the tip and the adsorbate. The disadvantage of this method is that it is experimentally very challenging to create and identify a junction with exactly one molecule between the electrodes.

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Muon

Muon	
	
The Moon's cosmic ray shadow, as seen in secondary muons generated by cosmic rays in the atmosphere, and detected 700 meters below ground, at the Soudan II detector.	
Composition:	Elementary particle
Particle statistics:	Fermionic
Group:	Lepton
Generation:	Second
Interaction:	Gravity, Electromagnetic, Weak
Symbol(s):	μ^-
Antiparticle:	Antimuon (μ^+)
Theorized:	—
Discovered:	Carl D. Anderson (1936)
Mass:	$105.65836668(38) \text{ MeV}/c^2$
Mean lifetime:	$2.197034(21) \times 10^{-6} \text{ s}^{[1]}$
Electric charge:	-1 e
Color charge:	None
Spin:	$\frac{1}{2}$

The **muon** (from the Greek letter mu (μ) used to represent it) is an elementary particle similar to the electron, with a negative electric charge and a spin of $\frac{1}{2}$. Together with the electron, the tau, and the three neutrinos, it is classified as a lepton. It is an unstable subatomic particle with the second longest mean lifetime ($2.2 \mu\text{s}$), exceeded only by that of the free neutron (~ 15 minutes). Like all elementary particles, the muon has a corresponding antiparticle of opposite charge but equal mass and spin: the **antimuon** (also called a *positive muon*). Muons are denoted by μ^- and antimuons by μ^+ . Muons were previously called **mu mesons**, but are not classified as mesons by modern particle physicists (see *History*).

Muons have a mass of $105.7 \text{ MeV}/c^2$, which is about 200 times the mass of an electron. Since the muon's interactions are very similar to those of the electron, a muon can be thought of as a much heavier version of the electron. Due to their greater mass, muons are not as sharply accelerated when they encounter electromagnetic fields, and do not emit as much bremsstrahlung radiation. Thus muons of a given energy penetrate matter far more deeply than electrons, since the deceleration of electrons and muons is primarily due to energy loss by this mechanism. So-called "secondary muons", generated by cosmic rays hitting the atmosphere, can penetrate to the Earth's surface

and into deep mines.

As with the case of the other charged leptons, the muon has an associated muon neutrino. Muon neutrinos are denoted by ν_μ .

History

Muons were discovered by Carl D. Anderson and Seth Neddermeyer at Caltech in 1936, while studying cosmic radiation. Anderson had noticed particles that curved differently from electrons and other known particles when passed through a magnetic field. They were negatively charged but curved less sharply than electrons, but more sharply than protons, for particles of the same velocity. It was assumed that the magnitude of their negative electric charge was equal to that of the electron, and so to account for the difference in curvature, it was supposed that their mass was greater than an electron but smaller than a proton. Thus Anderson initially called the new particle a *mesotron*, adopting the prefix *meso-* from the Greek word for "mid-". Shortly thereafter, additional particles of intermediate mass were discovered, and the more general term *meson* was adopted to refer to any such particle. To differentiate between different types of mesons, the mesotron was in 1947 renamed the *mu meson* (the Greek letter μ (*mu*) corresponds to *m*).

It was soon found that the mu meson significantly differed from other mesons: for example, its decay products included a neutrino and an antineutrino, rather than just one or the other, as was observed with other mesons. Other mesons were eventually understood to be hadrons—that is, particles made of quarks—and thus subject to the residual strong force. In the quark model, a *meson* is composed of exactly two quarks (a quark and antiquark) unlike baryons, which are composed of three quarks. Mu mesons, however, were found to be fundamental particles (leptons) like electrons, with no quark structure. Thus, mu mesons were not mesons at all (in the new sense and use of the term *meson*), and so the term *mu meson* was abandoned, and replaced with the modern term *muon*.

Another particle (the pion, with which the muon was initially confused) had been predicted by theorist Hideki Yukawa:^[2]

"It seems natural to modify the theory of Heisenberg and Fermi in the following way. The transition of a heavy particle from neutron state to proton state is not always accompanied by the mission of light particles. The transition is sometimes taken up by another heavy particle."

The existence of the muon was confirmed in 1937 by J. C. Street and E. C. Stevenson's cloud chamber experiment.^[3] The discovery of the muon seemed so incongruous and surprising at the time that Nobel laureate I. I. Rabi famously quipped, "Who ordered that?"

In a 1941 experiment on Mount Washington in New Hampshire, muons were used to observe the time dilation predicted by special relativity for the first time.^[4]

Muon sources

Since the production of muons requires an available center of momentum frame energy of 105.7 MeV, neither ordinary radioactive decay events nor nuclear fission and fusion events (such as those occurring in nuclear reactors and nuclear weapons) are energetic enough to produce muons. Only nuclear fission produces single-nuclear-event energies in this range, but do not produce muons as the production of a single muon would violate the conservation of quantum numbers (see under "muon decay" below).

On Earth, most naturally occurring muons are created by cosmic rays, which consist mostly of protons, many arriving from deep space at very high energy.^[5]

About 10,000 muons reach every square meter of the earth's surface a minute; these charged particles form as by-products of cosmic rays colliding with molecules in the upper atmosphere. Travelling at relativistic speeds, muons can penetrate tens of meters into rocks and other matter before attenuating as a result of absorption or deflection by other atoms.

— Mark Wolverton (September 2007). "Muons for Peace: New Way to Spot Hidden Nukes Gets Ready to Debut" ^[6]. *Scientific American* **297** (3): 26–28.

When a cosmic ray proton impacts atomic nuclei of air atoms in the upper atmosphere, pions are created. These decay within a relatively short distance (meters) into muons (the pion's preferred decay product), and neutrinos. The muons from these high energy cosmic rays generally continue in about the same direction as the original proton, at a very high velocity. Although their lifetime *without* relativistic effects would allow a half-survival distance of only about 0.66 km (660 meters) at most (as seen from Earth) the time dilation effect of special relativity (from the viewpoint of the Earth) allows cosmic ray secondary muons to survive the flight to the Earth's surface, since in the Earth frame, the muons have a longer half-life due to their velocity. From the viewpoint (inertial frame) of the muon, on the other hand, it is the length contraction effect of special relativity which allows this penetration, since in the muon frame, its lifetime is unaffected, but the distance through the atmosphere and earth appears far shorter than these distances in the Earth rest-frame. Both are equally valid ways of explaining the fast muon's unusual survival over distances.

Since muons are unusually penetrative of ordinary matter, like neutrinos, they are also detectable deep underground (700 meters at the Soudan II detector) and underwater, where they form a major part of the natural background ionizing radiation. Like cosmic rays, as noted, this secondary muon radiation is also directional.

The same nuclear reaction described above (i.e. hadron-hadron impacts to produce pion beams, which then quickly decay to muon beams over short distances) is used by particle physicists to produce muon beams, such as the beam used for the muon $g - 2$ experiment. ^[7]

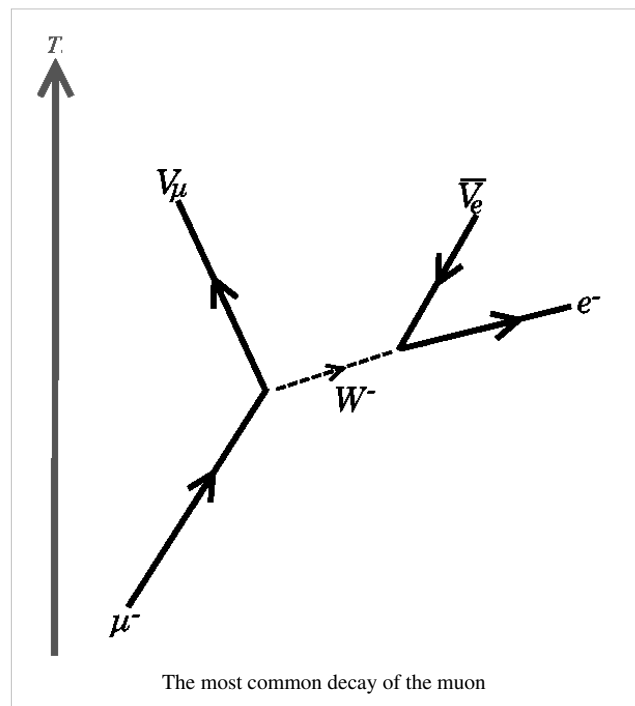
Muon decay

Muons are unstable elementary particles and are heavier than electrons and neutrinos but lighter than all other matter particles. They decay via the weak interaction. Because lepton numbers must be conserved, one of the product neutrinos of muon decay must be a muon-type neutrino and the other an electron-type antineutrino (antimuon decay produces the corresponding antiparticles, as detailed below). Because charge must be conserved, one of the products of muon decay is always an electron of the same charge as the muon (a positron if it is a positive muon). Thus all muons decay to at least an electron, and two neutrinos. Sometimes, besides these necessary products, additional other particles that have a net charge and spin of zero (i.e. a pair of photons, or an electron-positron pair), are produced.

The dominant muon decay mode (sometimes called the Michel decay after Louis Michel) is the simplest possible: the muon decays to an electron, an electron-antineutrino, and a muon-neutrino. Antimuons, in mirror fashion, most often decay to the corresponding antiparticles: a positron, an electron-neutrino, and a muon-antineutrino. In formulaic terms, these two decays are:

$$\mu^- \rightarrow e^- + \bar{\nu}_e + \nu_\mu, \quad \mu^+ \rightarrow e^+ + \nu_e + \bar{\nu}_\mu.$$

The mean lifetime of the (positive) muon is $2.197\,019 \pm 0.000\,021 \mu\text{s}$ ^[8]. The equality of the muon and anti-muon lifetimes has been established to better than one part in 10^4 .



The tree-level muon decay width is

$$\Gamma = \frac{G_F^2 m_\mu^5}{192\pi^3} I\left(\frac{m_e^2}{m_\mu^2}\right),$$

where $I(x) = 1 - 8x - 12x^2 \ln x + 8x^3 - x^4$; G_F^2 is the Fermi coupling constant.

The decay distributions of the electron in muon decays have been parameterised using the so-called Michel parameters. The values of these four parameters are predicted unambiguously in the Standard Model of particle physics, thus muon decays represent a good test of the space-time structure of the weak interaction. No deviation from the Standard Model predictions has yet been found.

Certain neutrino-less decay modes are kinematically allowed but forbidden in the Standard Model. Examples forbidden by lepton flavour conservation are

$$\mu^- \rightarrow e^- + \gamma \text{ and } \mu^- \rightarrow e^- + e^+ + e^-.$$

Observation of such decay modes would constitute clear evidence for physics beyond the Standard Model (BSM). Current experimental upper limits for the branching fractions of such decay modes are in the range 10^{-11} to 10^{-12} .

Muonic atoms

The muon was the first elementary particle discovered that does not appear in ordinary atoms. Negative muons can, however, form muonic atoms (also called mu-mesic atoms), by replacing an electron in ordinary atoms. Muonic *hydrogen* atoms are much smaller than typical hydrogen atoms because the much larger mass of the muon gives it a much smaller ground-state wavefunction than is observed for the electron. In multi-electron atoms, when only one of the electrons is replaced by a muon, the size of the atom continues to be determined by the other electrons, and the atomic size is nearly unchanged. However, in such cases the orbital of the muon continues to be smaller and far closer to the nucleus than the atomic orbitals of the electrons.

A positive muon, when stopped in ordinary matter, can also bind an electron and form an exotic atom known as muonium (Mu) atom, in which the muon acts as the nucleus. The positive muon, in this context, can be considered a pseudo-isotope of hydrogen with one ninth of the mass of the proton. Because the reduced mass of muonium, and hence its Bohr radius, is very close to that of hydrogen, this short-lived "atom" behaves chemically — to a first approximation — like hydrogen, deuterium and tritium.

Use in measurement of the proton charge radius

The recent culmination of a twelve year experiment^[9] investigating the proton's charge radius involved the use of muonic hydrogen. This form of hydrogen is composed of a muon orbiting a proton^[10]. The Lamb shift in muonic hydrogen was measured by driving the muon from the from its 2s state up to an excited 2p state using a laser^[11]. The frequency of the photon required to induce this transition was revealed to be 50 terahertz which, according to present theories of quantum electrodynamics, yields a value of 0.84184 ± 0.00067 femtometres for the charge radius of the proton.^[12]

Anomalous magnetic dipole moment

The anomalous magnetic dipole moment is the difference between the experimentally observed value of the magnetic dipole moment and the theoretical value predicted by the Dirac equation. The measurement and prediction of this value is very important in the precision tests of QED (quantum electrodynamics). The E821 experiment^[13] at Brookhaven National Laboratory (BNL) studied the precession of muon and anti-muon in a constant external magnetic field as they circulated in a confining storage ring. The E821 Experiment reported the following average value (from the July 2007 review by Particle Data Group)^[14]

$$a = \frac{g-2}{2} = 0.00116592080(54)(33)$$

where the first errors are statistical and the second systematic.

The difference between the g -factors of the muon and the electron is due to their difference in mass. Because of the muon's larger mass, contributions to the theoretical calculation of its anomalous magnetic dipole moment from Standard Model weak interactions and from contributions involving hadrons are important at the current level of precision, whereas these effects are not important for the electron. The muon's anomalous magnetic dipole moment is also sensitive to contributions from new physics beyond the Standard Model, such as supersymmetry. For this reason, the muon's anomalous magnetic moment is normally used as a probe for new physics beyond the Standard Model rather than as a test of QED (Phys.Lett. B649, 173 (2007) ^[15]).

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External links

- Muon anomalous magnetic moment and supersymmetry (<http://antwpr.gsfc.nasa.gov/apod/ap050828.html>)
- g-2 (muon anomalous magnetic moment) experiment (<http://www.g-2.bnl.gov/>)
- muLan (Measurement of the Positive Muon Lifetime) experiment (<http://www.npl.uiuc.edu/exp/mulan/>)
- The Review of Particle Physics (<http://pdg.lbl.gov/>)
- The TRIUMF Weak Interaction Symmetry Test (<http://twist.triumf.ca/>)

Ionization cooling

Physical Principle

Ionization cooling is a process by which the beam emittance of a beam of particles may be reduced ^[1]. In ionization cooling, particles are passed through some material. The momentum of the particles is reduced as they ionize atomic electrons in the material. Thus the normalised beam emittance is reduced. By re-accelerating the beam, for example in an RF cavity, the longitudinal momentum may be restored without replacing transverse momentum. Thus overall the angular spread and hence the geometric emittance in the beam will be reduced.

Ionization cooling can be spoiled by stochastic physical processes. Multiple Coulomb scattering in muons as well as nuclear scattering in protons and ions can reduce the cooling or even lead to net heating transverse to the direction of beam motion. In addition, energy straggling can cause heating parallel to the direction of beam motion.

Muon Cooling

The primary use of ionization cooling is envisaged to be for cooling of muon beams. This is because ionization cooling is the only technique that works on the timescale of the muon lifetime. Ionization cooling channels have been designed for use in a Neutrino Factory and a Muon Collider. Muon ionization cooling is expected to be demonstrated for the first time by the Proof of Principle International Muon Ionization Cooling Experiment. Other PoP muon ionization cooling experiments have been devised.

Other Particles

Ionization cooling has also been proposed for use in low energy ion beams and proton beams.

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ISIS neutron source

ISIS is a pulsed neutron and muon source. It is situated at the Rutherford Appleton Laboratory on the Harwell Science and Innovation Campus in Oxfordshire, United Kingdom and is part of the Science and Technology Facilities Council. It uses the techniques muon spectroscopy and neutron scattering to probe the structure and dynamics of condensed matter on a microscopic scale ranging from the subatomic to the macromolecular.

Hundreds of experiments are performed annually at ISIS by visiting researchers from around the world, in diverse science areas including physics, chemistry, materials engineering, earth sciences, biology and archaeology.

Neutrons and muons

Neutrons are uncharged constituents of atoms and penetrate materials well, deflecting only from the nuclei of atoms. The statistical accumulation of deflected neutrons at different positions beyond the sample can be used to find the structure of a material, and the loss or gain of energy by neutrons can reveal the dynamic behaviour of parts of a sample, for example diffusive processes in solids. At ISIS the neutrons are created by accelerating 'bunches' of protons in a synchrotron, then colliding these with a heavy tantalum metal target, under a constant cooling load to dissipate the heat from the 160 kW proton beam. The impacts cause neutrons to spall off the tantalum atoms, and the neutrons are channelled through guides, or beamlines, to about 20 instruments, individually optimised for the study of different types of matter. The target station and most of the instruments are set in a large hall. Neutrons are a dangerous form of radiation, so the target and beamlines are heavily shielded with concrete.

ISIS produces muons by colliding a fraction of the proton beam with a graphite target, producing pions which decay rapidly into muons, delivered in a spin-polarised beam to sample stations.



ISIS experimental hall for Target Station 1

Science at ISIS

ISIS is administered and operated by the Science and Technology Facilities Council (previously CCLRC). Experimental time is open to academic users from funding countries and is applied for through a twice-yearly 'call for proposals'. Research allocation, or 'beam-time', is allotted to applicants via a peer-review process. Users and their parent institutions do not pay for

the running costs of the facility, which are as much as £11,000 per instrument per day. Their transport and living costs are also refunded whilst carrying out the experiment. Most users stay in Ridgeway House, a hotel near the site, or at Cosener's House, an STFC-run conference centre in Abingdon. Over 600 experiments by 1600 users are completed every year.

A large number of support staff operate the facility, aid users, and carry out research, the control room is staffed 24 hours a day, every day of the year. Instrument scientists oversee the running of each instrument and liaise with users, and other divisions provide sample environment, data analysis and computing expertise, maintain the accelerator, and run education programmes.

Among the important and pioneering work carried out was the discovery of the structure of high-temperature superconductors and the solid phase of buckminsterfullerene.

Construction for a second target station started in 2003, and the first neutrons were delivered to the target on December 14, 2007^[1]. It will use low-energy neutrons to study soft condensed matter, biological systems, advanced composites and nanomaterials. To supply the extra protons for this, the accelerator is being upgraded.

History and background of ISIS

The source was approved in 1977 for the RAL site on the Harwell campus and recycled components from earlier UK science programmes including the accelerator hall which had previously been occupied by the Nimrod accelerator. The first beam was produced in 1984, and the facility was formally opened by the then Prime Minister Margaret Thatcher in October 1985.^[2]

The name ISIS is not an acronym: it refers to the Ancient Egyptian goddess and the local name for the River Thames. The name was selected for the official opening of the facility in 1985, prior to this it was known as the SNS, or Spallation Neutron Source. The name was considered appropriate as Isis was a goddess who could restore life to the dead, and ISIS made use of equipment previously constructed for the Nimrod and Nina accelerators^[3].



Another view of the ISIS experimental hall for Target Station 1

External links

- ISIS facility ^[4]
- ISIS Second Target Station ^[5]
- The Science and Technology Facilities Council ^[6]

References

- [1] ISIS Second Target Station Project (<http://ts-2.isis.rl.ac.uk/>)
- [2] Linacs at the Rutherford Appleton Laboratory (<http://epubs.cclrc.ac.uk/bitstream/692/linacplahistory.pdf>)
- [3] Explanation of the name of ISIS (<http://www.isis.rl.ac.uk/aboutIsis/index.htm>)
- [4] <http://www.isis.stfc.ac.uk/>
- [5] <http://www.isis.stfc.ac.uk/about-isis/target-station-2/>
- [6] <http://www.stfc.ac.uk>

Geographical coordinates: 51°34'18"N 1°19'12"W

Neutron spin echo

Neutron spin echo spectroscopy is an inelastic neutron scattering technique invented by Ferenc Mezei in the 1970's, and developed in collaboration with John Hayter. ^[1] In recognition of his work and in other areas, Mezei was awarded the first Walter Haelg Prize ^[2] in 1999.

The spin-echo spectrometer possesses an extremely high energy resolution (roughly one part in 100,000). Additionally, it measures the density-density correlation (or intermediate scattering function) $F(Q,t)$ as a function of momentum transfer Q and time. Other neutron scattering techniques measure the dynamic structure factor $S(Q,\omega)$, which can be converted to $F(Q,t)$ by a Fourier transform, which may be difficult in practice. For weak inelastic features $S(Q,\omega)$ is better suited, however, for (slow) relaxations the natural representation is given by $F(Q,t)$. Because of its extraordinary high effective energy resolution compared to other neutron scattering techniques, NSE is an ideal method to observe ^[3] overdamped internal dynamic modes (relaxations) and other diffusive processes in materials such as a polymer blends, alkane chains, or microemulsions. The extraordinary power of NSE spectrometry was further demonstrated recently^{[4] [5]} by the direct observation of coupled internal protein domain dynamics in the proteins NHERF1 and Taq polymerase, allowing the direct visualization of protein nanomachinery in motion.

How it works

Basically NSE is a time-of-flight technique. Concerning the neutron spins it has a strong analogy to the so-called Hahn echo,^[6] well known in the field of NMR. In both cases the loss of polarization (magnetization) due to dephasing of the spins in time is restored by an effective time reversal operation, that leads to a restitution of polarization (rephasing). In NMR the dephasing happens due to variation in the local fields at positions of the nuclei, in NSE the dephasing is due to different neutron velocities in the incoming neutron beam. The Larmor precession of the neutron spin in a preparation zone with a magnetic field before the sample encodes the individual velocities of neutrons in the beam into precession angles. Close to the sample the time reversal is effected by a so-called flipper. A symmetric decoding zone follows such that at its end the precession angle accumulated in the preparation zone is exactly compensated (provided the sample did not change the neutron velocity, i.e. elastic scattering), all spins rephase to form the "spin-echo". Ideally the full polarization is restored. This effect does not depend on the velocity/energy/wavelength of the incoming neutron. If the scattering at the sample is not elastic but changes the neutron velocity, the rephasing will become incomplete and a loss of final polarization results, which depends on the distribution of differences in the time, which the neutrons need to fly through the symmetric first (coding) and second (decoding) precession zones. The time differences occur due to a velocity change acquired by non-elastic

scattering at the sample. The distribution of these time differences is proportional (in the linearization approximation which is appropriate for quasi-elastic high resolution spectroscopy) to the spectral part of the scattering function $S(Q, \omega)$. The effect on the measured beam polarization is proportional to the cos-Fourier transform of the spectral function, the intermediate scattering function $F(Q, t)$. The time parameter depends on the neutron wavelength and the factor connecting precession angle with (reciprocal) velocity, which can e.g. be controlled by setting a certain magnetic field in the preparation and decoding zones. Scans of t may then be performed by varying the magnetic field. For some further explanations pertaining the NSE principle with animations see: pathfinder.neutron-eu.net ^[7].

It is important to note: all the spin manipulations are just a means to detect velocity changes of the neutron, which influence --for technical reasons-- in terms of a Fourier transform of the spectral function in the measured intensity. The velocity changes of the neutrons convey the physical information which is available by using NSE, i.e.

$$I(Q, t) \propto S(Q) + \int \cos(\omega t) S(Q, \omega) d\omega \text{ where } \omega \propto \Delta v \text{ and } t \propto B \times \lambda^3.$$

B denotes the precession field strength, λ the (average) neutron wavelength and Δv the neutron velocity change upon scattering at the sample.

The main reason for using NSE is that by the above means it can reach Fourier times of up to many 100ns, which corresponds to energy resolutions in the neV range. The closest approach to this resolution by a spectroscopic neutron instrument type, namely the backscattering spectrometer (BSS), is in the range of 0.5 to 1 μ eV. The spin-echo trick allows to use an intense beam of neutrons with a wavelength distribution of 10% or more and at the same time to be sensitive to velocity changes in the range of less than 10^{-4} .

Note: the above explanations assumes the generic NSE configuration --as first utilized by the IN11 instrument at the Institut Laue–Langevin (ILL)--. Other approaches are possible like the resonance spin-echo, NRSE with concentrated a DC field and a RF field in the flippers at the end of preparation and decoding zones which then are without magnetic field (zero field). In principle these approaches are equivalent concerning the connection of the final intensity signal with the intermediate scattering function. Due to technical difficulties until now they have not reached the same level of performance than the generic (IN11) NSE types.

What it can measure

In soft matter research the structure of macromolecular objects is often investigated by small angle neutron scattering, SANS. The exchange of hydrogen with deuterium in some of the molecules creates scattering contrast between even equal chemical species. The SANS diffraction pattern—if interpreted in real space—corresponds to a snapshot picture of the molecular arrangement. Neutron spin echo instruments can analyze the inelastic broadening of the SANS intensity and thereby analyze the motion of the macromolecular objects. ^[8] A coarse analogy would be a photo with a certain opening time instead of the SANS like snapshot. The opening time corresponds to the Fourier time which depends on the setting of the NSE spectrometer, it is proportional to the magnetic field (integral) and to the third power of the neutron wavelength. Values up to several hundreds of nanoseconds are available. Note that the spatial resolution of the scattering experiment is in the nanometer range, which means that a time range of e.g. 100 ns corresponds to effective molecular motion velocities of 1 nm/100 ns = 1 cm/s. This may be compared to the typical neutron velocity of 200..1000 m/s used in these type of experiments.

NSE and spin-incoherent scattering (from protons)

Many inelastic studies that use normal time-of-flight (TOF) or backscattering spectrometers rely on the huge incoherent neutron scattering cross section of protons. The scattering signal is dominated by the corresponding contribution, which represents the (average) self-correlation function (in time) of the protons.

For NSE spin incoherent scattering has the disadvantage that it flips the neutron spins during scattering with a probability of 2/3. Thus converting 2/3 of the scattering intensity into "non-polarized" background and putting a factor of -1/3 in front of the cos-Fourier integral contribution pertaining the incoherent intensity. This signal subtracts from the coherent echo signal. The result may be a complicated combination which cannot be decomposed if only NSE is employed. However, in pure cases, i.e. when there is an overwhelming intensity contribution due to protons, NSE can be used to measure their incoherent spectrum.

The intensity situation of NSE --for e.g. soft-matter samples-- is the same as in small angle scattering (SANS). Which means that molecular objects with coherent scattering contrast at low Q (momentum transfer) show a much larger intensity as the incoherent contribution (which is the background level). But at larger Q usually somewhere around $Q=0.3 \text{ \AA}^{-1}$ the incoherent scattering becomes stronger than the coherent part. At least for hydrogen containing systems contrast requires the presense of some protons and even pure deuterated samples show spin-incoherent scattering from deuterons, however, 40 times weaker than the proton scattering.

Fully protonated samples allow successful measurements but at intensities of the order of the SANS background level.^[9] This requires correspondingly long counting times.

Note: This interference with the spin manipulation of the NSE technique occurs only with **spin-incoherent** scattering. Isotopic incoherent scattering yields a "normal" NSE signal.

Existing spectrometers

- IN11^[10] (Institut Laue-Langevin, ILL^[11], Grenoble, France)
- IN15^[12] (Institut Laue-Langevin, ILL^[11], Grenoble, France)
- J-NSE (Juelich Centre for Neutron Science JCNS^[13], Juelich, Germany, hosted by FRMII^[14], Munich (Garching), Germany)
- NG5-NSE (NIST CNRF^[15], Gaithersburg, USA)
- NSE@SNS (JCNS^[16] SNS, Oak Ridge^[17])
- RESEDA (FRM II Munich FRMII^[14], Munich, Germany)
- V5/SPAN (Hahn-Meitner Institut^[18], Berlin, Germany)
- C2-2 (ISSP^[19], Tokai, Japan)

See also

- Biological small-angle scattering
- Larmor precession
- Neutron resonance spin echo
- Neutron scattering
- NMR
- Protein domain
- SAXS
- Soft matter
- Spin echo

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- [11] <http://www.ill.fr>
- [12] <http://www.ill.eu/in15/>
- [13] <http://www.jcns.info>
- [14] <http://wwwnew.frm2.tum.de>
- [15] <http://www.ncnr.nist.gov>
- [16] http://www.jcns.info/jcns_nse_sns
- [17] <http://neutrons.ornl.gov/instruments/SNS/NSE/>
- [18] <http://www.hmi.de>
- [19] <http://www.issp.u-tokyo.ac.jp>

Hadron spectroscopy

Hadron spectroscopy is the subfield of particle physics that studies the masses and decays of hadrons. Hadron spectroscopy is also an important part of the new nuclear physics. The properties of hadrons are a consequence of a theory called quantum chromodynamics (QCD).

QCD predicts that quarks and antiquarks bind into particles called mesons. Another type of hadron is called a baryon, that is made of three quarks. There is good experimental evidence for both mesons and baryons. Potentially QCD also has bound states of just gluons called glueballs. One of the goals of the field of hadronic spectroscopy is to find experimental evidence for exotic mesons, tetraquarks, molecules of hadrons, and glueballs.

An important part of the field of hadronic spectroscopy are the attempts to solve QCD. The properties of hadrons require the solution of QCD in the strong coupling regime, where perturbative techniques based on Feynman diagrams do not work. There are several approaches to trying to solve QCD to compute the masses of hadrons:

- Quark models ^[1]
- Lattice QCD
- Effective field theory
- sum rules ^[2]

Experimental facilities

- Jefferson Lab ^[3] in the US.
- J-PARC ^[4] in Japan.
- GSI ^[5] Darmstadt Germany.
- COMPASS ^[6] CERN, Switzerland.

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 [5] <http://www.gsi.de/>
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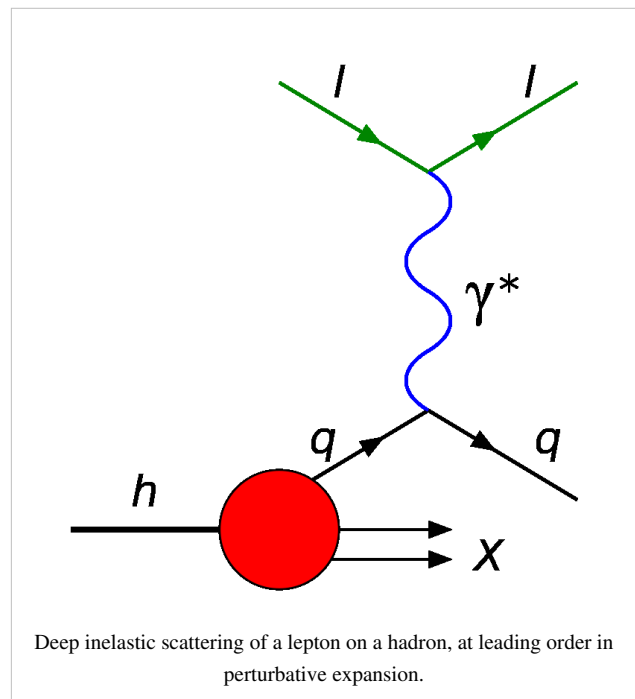
Deep inelastic scattering

Deep inelastic scattering is the name given to a process used to probe the insides of hadrons (particularly the baryons, such as protons and neutrons), using electrons, muons and neutrinos. It provided the first convincing evidence of the reality of quarks, which up until that point had been considered by many to be a purely mathematical phenomenon. It is a relatively new process, first attempted in the 1960s and 1970s. It is conceptually similar to Rutherford Scattering, but with important differences. ^[1]

Quarks

The Standard Model of physics, particularly given the work of Murray Gell-Mann in the 1960s, had been successful in uniting much of the previously disparate concepts in particle physics into one, relatively straightforward, scheme. In essence, there were three types of particles.

- The leptons, which were light (as in not particularly massive) particles such as electrons, neutrinos and their antiparticles. They have integer charge
- The bosons, which were particles that exchange forces. These ranged from the massless, easy-to-detect photon (the carrier of the electro-magnetic force) to the exotic (though still massless) gluons that carry the strong nuclear force



- The quarks, which were massive particles that carried fractional charges. They are the "building blocks" of the hadrons. They are also the only particles to be affected by the strong interaction

The leptons had been detected since 1897, when J. J. Thomson had shown that electric current is a flow of electrons. Some bosons were being routinely detected, although the W^+ , W^- and Z^0 particles of the electroweak force were only categorically seen in the early 1980s, and gluons were only firmly pinned down at DESY in Hamburg at about the same time. Quarks, however, were still elusive.

The experiments

Drawing on Rutherford's groundbreaking experiments in the early years of the Twentieth century, ideas for detecting quarks were formulated. Rutherford had proven that atoms had a small, massive, charged nucleus at their centre by firing alpha particles at atoms in gold. Most had gone through with little or no deviation, but a few were deflected through large angles or came right back. This suggested that atoms had internal structure, and a lot of empty space.

In order to enter baryons (where quarks were theoretically to be found), a small, penetrating (ie easily accelerated; in reality this meant charged) and easily produced particle needed to be found. Electrons were considered ideal for the role, and in a series of remarkable technological and engineering leaps, electrons were fired at protons and neutrons in atomic nuclei. As an added bonus, the electrostatic attraction of the positively charged nucleus and the negatively charged electron increased the speed. Later experiments were conducted with muons, but the same principles apply.

The collision absorbs some kinetic energy, and as such it is inelastic (this compares to Rutherford scattering which is elastic, with no loss of kinetic energy, taking into account recoils of the nuclei). The electron emerges from the nucleus, and its trajectory and velocity can be detected.

Analysis of the results led to the following conclusions:

- The hadrons do have internal structure
- In baryons, there are three points of deflection (i.e. baryons consist of three quarks)
- In mesons, there are two points of deflection (i.e. mesons consist of a quark and an anti-quark. The reason they do not consist of two quarks is to do with their colour; see the quark article for more explanation)
- Quarks appear to be point charges, as electrons appear to be, with the fractional charges suggested by the Standard Model

The experiments were important because, not only did they confirm the physical reality of quarks but also proved again that the Standard Model was the correct avenue of research for particle physicists to pursue.

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Imaging

Ultrasound imaging

Diagnostic sonography (ultrasonography) is an ultrasound-based diagnostic imaging technique used for visualizing subcutaneous body structures including tendons, muscles, joints, vessels and internal organs for possible pathology or lesions. Obstetric sonography is commonly used during pregnancy and is widely recognized by the public.

In physics, the term "ultrasound" applies to all acoustic energy (longitudinal, mechanical wave) with a frequency above the audible range of human hearing. The audible range of sound is 20 hertz-20 kilohertz. Ultrasound is frequency greater than 20 kilohertz.

Diagnostic applications

Typical diagnostic sonographic scanners operate in the frequency range of 1 to 18 megahertz, though frequencies up to 50-100 megahertz has been used experimentally in a technique known as biomicroscopy in special regions, such as the anterior chamber of eye. The above frequencies are hundreds of times greater than the limit of human hearing, which is typically accepted as 20 kilohertz. The choice of frequency is a trade-off between spatial resolution of the image and imaging depth: lower frequencies produce less resolution but image deeper into the body.

Sonography (ultrasonography) is widely used in medicine. It is possible to perform both diagnosis and therapeutic procedures, using ultrasound to guide interventional procedures (for instance biopsies or drainage of fluid collections). Sonographers are medical professionals who perform scans for diagnostic purposes. Sonographers typically use a hand-held probe (called a transducer) that is placed directly on and moved over the patient.

Sonography is effective for imaging soft tissues of the body. Superficial structures such as muscles, tendons, testes, breast and the neonatal brain are imaged at a higher frequency (7-18 MHz), which provides better axial and lateral resolution. Deeper structures such as liver and kidney are imaged at a lower frequency 1-6 MHz with lower axial and lateral resolution but greater penetration.

Medical sonography is used in the study of many different systems:



Orthogonal planes of a 3 dimensional sonographic volume with transverse and coronal measurements for estimating fetal cranial volume. ^[1] ^[2]

System	Description	See also
Cardiology	Echocardiography is an essential tool in cardiology, to diagnose e.g. dilatation of parts of the heart and function of heart ventricles and valves	see echocardiography
Emergency Medicine	Point of care ultrasound has many applications in the Emergency Department, including the Focused Assessment with Sonography for Trauma (FAST) exam for assessing significant hemoperitoneum or pericardial tamponade after trauma. Ultrasound is routinely used in the Emergency Department to expedite the care of patients with right upper quadrant abdominal pain who may have gallstones or cholecystitis.	see FAST exam
Gastroenterology	In abdominal sonography, the solid organs of the abdomen such as the pancreas, aorta, inferior vena cava, liver, gall bladder, bile ducts, kidneys, and spleen are imaged. Sound waves are blocked by gas in the bowel and attenuated in different degree by fat, therefore there are limited diagnostic capabilities in this area. The appendix can sometimes be seen when inflamed e.g.: appendicitis.	
Gynecology		see gynecologic ultrasonography
Neurology	for assessing blood flow and stenoses in the carotid arteries (Carotid ultrasonography) and the big intracerebral arteries	see Carotid ultrasonography. Intracerebral: see Transcranial Doppler
Obstetrics	Obstetrical ultrasound is commonly used during pregnancy to check on the development of the fetus.	see obstetric ultrasonography
Ophthalmology		see A-scan ultrasonography, B-scan ultrasonography
Urology	to determine, for example, the amount of fluid retained in a patient's bladder. In a pelvic sonogram, organs of the pelvic region are imaged. This includes the uterus and ovaries or urinary bladder. Men are sometimes given a pelvic sonogram to check on the health of their bladder and prostate. There are two methods of performing a pelvic sonography - externally or internally. The internal pelvic sonogram is performed either transvaginally (in a woman) or transrectally (in a man). Sonographic imaging of the pelvic floor can produce important diagnostic information regarding the precise relationship of abnormal structures with other pelvic organs and it represents a useful hint to treat patients with symptoms related to pelvic prolapse, double incontinence and obstructed defecation. ^[3]	
Musculoskeletal	tendons, muscles, nerves, ligaments, soft tissue masses, and bone surfaces	
Cardiovascular system	To assess patency and possible obstruction of arteries Arterial sonography, diagnose DVT (Thrombosonography) and determine extent and severity of venous insufficiency (venosonography)	Intravascular ultrasound

Other types of uses include:

- Interventional; biopsy, emptying fluids, intrauterine transfusion (Hemolytic disease of the newborn)
- Contrast-enhanced ultrasound

A general-purpose sonographic machine may be used for most imaging purposes. Usually specialty applications may be served only by use of a specialty transducer. Most ultrasound procedures are done using a transducer on the surface of the body, but improved diagnostic confidence is often possible if a transducer can be placed inside the body. For this purpose, specialty transducers, including endovaginal, endorectal, and transesophageal transducers are commonly employed. At the extreme of this, very small transducers can be mounted on small diameter catheters and placed into blood vessels to image the walls and disease of those vessels.

Therapeutic applications

Therapeutic applications use ultrasound to bring heat or agitation into the body. Therefore much higher energies are used than in diagnostic ultrasound. In many cases the range of frequencies used are also very different.

- Ultrasound is sometimes used to clean teeth in dental hygiene.
- Ultrasound sources may be used to generate regional heating and mechanical changes in biological tissue, e.g. in occupational therapy, physical therapy and cancer treatment. However the use of ultrasound in the treatment of musculoskeletal conditions has fallen out of favor.^{[4] [5]}
- Focused ultrasound may be used to generate highly localized heating to treat cysts and tumors (benign or malignant). This is known as Focused Ultrasound Surgery (FUS) or High Intensity Focused Ultrasound (HIFU). These procedures generally use lower frequencies than medical diagnostic ultrasound (from 250 kHz to 2000 kHz), but significantly higher energies. HIFU treatment is often guided by MRI.
- Focused ultrasound may be used to break up kidney stones by lithotripsy.
- Ultrasound may be used for cataract treatment by phacoemulsification.
- Additional physiological effects of low-intensity ultrasound have recently been discovered, e.g. its ability to stimulate bone-growth and its potential to disrupt the blood-brain barrier for drug delivery.
- Procoagulant at 5-12 MHz,

From sound to image

The creation of an image from sound is done in three steps - producing a sound wave, receiving echoes, and interpreting those echoes.

Producing a sound wave

A sound wave is typically produced by a piezoelectric transducer encased in a housing which can take a number of forms. Strong, short electrical pulses from the ultrasound machine make the transducer ring at the desired frequency. The frequencies can be anywhere between 2 and 18 MHz. The sound is focused either by the shape of the transducer, a lens in front of the transducer, or a complex set of control pulses from the ultrasound scanner machine (Beamforming). This focusing produces an arc-shaped sound wave from the face of the transducer. The wave travels into the body and comes into focus at a desired depth.

Older technology transducers focus their beam with physical lenses. Newer technology transducers use phased array techniques to enable the sonographic machine to change the direction and depth of focus. Almost all piezoelectric transducers are made of ceramic.

Materials on the face of the transducer enable the sound to be transmitted efficiently into the body (usually seeming to be a rubbery coating, a form of impedance matching). In addition, a water-based gel is placed between the patient's skin and the probe.

The sound wave is partially reflected from the layers between different tissues. Specifically, sound is reflected anywhere there are density changes in the body: e.g. blood cells in blood plasma, small structures in organs, etc. Some of the reflections return to the transducer.



Medical sonographic instrument

Receiving the echoes

The return of the sound wave to the transducer results in the same process that it took to send the sound wave, except in reverse. The return sound wave vibrates the transducer, the transducer turns the vibrations into electrical pulses that travel to the ultrasonic scanner where they are processed and transformed into a digital image.

Forming the image

The sonographic scanner must determine three things from each received echo:

1. How long it took the echo to be received from when the sound was transmitted.
2. From this the focal length for the phased array is deduced, enabling a sharp image of that echo at that depth (this is not possible while producing a sound wave).
3. How strong the echo was. It could be noted that sound wave is not a click, but a pulse with a specific carrier frequency. Moving objects change this frequency on reflection, so that it is only a matter of electronics to have simultaneous Doppler sonography.

Once the ultrasonic scanner determines these three things, it can locate which pixel in the image to light up and to what intensity and at what hue if frequency is processed (see redshift for a natural mapping to hue).

Transforming the received signal into a digital image may be explained by using a blank spreadsheet as an analogy. First picture a long, flat transducer at the top of the sheet. Send pulses down the 'columns' of the spreadsheet (A, B, C, etc.). Listen at each column for any return echoes. When an echo is heard, note how long it took for the echo to return. The longer the wait, the deeper the row (1,2,3, etc.). The strength of the echo determines the brightness setting for that cell (white for a strong echo, black for a weak echo, and varying shades of grey for everything in between.) When all the echoes are recorded on the sheet, we have a greyscale image.

Displaying the image

Images from the sonographic scanner can be displayed, captured, and broadcast through a computer using a frame grabber to capture and digitize the analog video signal. The captured signal can then be post-processed on the computer itself.^[6]

For computational details see also: Confocal laser scanning microscopy, Radar,

Sound in the body

Ultrasonography (sonography) uses a probe containing one or more acoustic transducers to send pulses of sound into a material. Whenever a sound wave encounters a material with a different density (acoustical impedance), part of the sound wave is reflected back to the probe and is detected as an echo. The time it takes for the echo to travel back to the probe is measured and used to calculate the depth of the tissue interface causing the echo. The greater the difference between acoustic impedances, the larger the echo is. If the pulse hits gases or solids, the density difference is so great that most of the acoustic energy is reflected and it becomes impossible to see deeper.

The frequencies used for medical imaging are generally in the range of 1 to 18 MHz. Higher frequencies have a correspondingly smaller wavelength, and can be used to make sonograms with smaller details. However, the attenuation of the sound wave is increased at higher frequencies, so in order to have better penetration of deeper tissues, a lower frequency (3-5 MHz) is used.



Linear Array Transducer

Seeing deep into the body with sonography is very difficult. Some acoustic energy is lost every time an echo is formed, but most of it (approximately $0.3 \frac{\text{dB}}{\text{cm depth} \cdot \text{MHz}}$) is lost from acoustic absorption.

The speed of sound varies as it travels through different materials, and is dependent on the acoustical impedance of the material. However, the sonographic instrument assumes that the acoustic velocity is constant at 1540 m/s. An effect of this assumption is that in a real body with non-uniform tissues, the beam becomes somewhat de-focused and image resolution is reduced.

To generate a 2D-image, the ultrasonic beam is swept. A transducer may be swept mechanically by rotating or swinging. Or a 1D phased array transducer may be used to sweep the beam electronically. The received data is processed and used to construct the image. The image is then a 2D representation of the slice into the body.

3D images can be generated by acquiring a series of adjacent 2D images. Commonly a specialised probe that mechanically scans a conventional 2D-image transducer is used. However, since the mechanical scanning is slow, it is difficult to make 3D images of moving tissues. Recently, 2D phased array transducers that can sweep the beam in 3D have been developed. These can image faster and can even be used to make live 3D images of a beating heart.

Doppler ultrasonography is used to study blood flow and muscle motion. The different detected speeds are represented in color for ease of interpretation, for example leaky heart valves: the leak shows up as a flash of unique color. Colors may alternatively be used to represent the amplitudes of the received echoes.

Modes of sonography

Several different modes of ultrasound are used in medical imaging.^[7] These are:

- **A-mode:** A-mode is the simplest type of ultrasound. A single transducer scans a line through the body with the echoes plotted on screen as a function of depth. Therapeutic ultrasound aimed at a specific tumor or calculus is also A-mode, to allow for pinpoint accurate focus of the destructive wave energy.
- **B-mode:** In B-mode ultrasound, a linear array of transducers simultaneously scans a plane through the body that can be viewed as a two-dimensional image on screen.
- **M-mode:** M stands for motion. In m-mode a rapid sequence of B-mode scans whose images follow each other in sequence on screen enables doctors to see and measure range of motion, as the organ boundaries that produce reflections move relative to the probe.
- **Doppler mode:** This mode makes use of the Doppler effect in measuring and visualizing blood flow
 - **Color doppler:** Velocity information is presented as a color coded overlay on top of a B-mode image
 - **Continuous doppler:** Doppler information is sampled along a line through the body, and all velocities detected at each time point is presented (on a time line)
 - **Pulsed wave (PW) doppler:** Doppler information is sampled from only a small sample volume (defined in 2D image), and presented on a timeline
 - **Duplex:** a common name for the simultaneous presentation of 2D and (usually) PW doppler information. (Using modern ultrasound machines color doppler is almost always also used, hence the alternative name **Triplex**.)

Midwives generally use this type of system.

Expansions

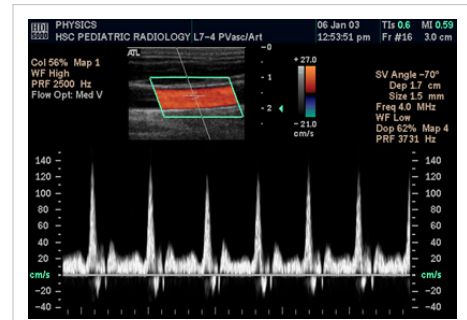
An additional expansion or additional technique of ultrasound is **biplanar ultrasound**, in which the probe has two 2D planes that are perpendicular to each other, providing more efficient localization and detection.^[8] Furthermore, an **omniplane** probe is one that can rotate 180° to obtain multiple images.^[8] In 3D ultrasound, many 2D planes are digitally added together to create a 3-dimensional image of the object. In contrast-enhanced ultrasound, microbubble contrast agents enhance the ultrasound waves, resulting in increased contrast.

Doppler sonography

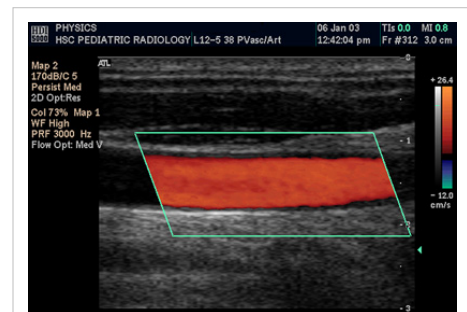
Sonography can be enhanced with Doppler measurements, which employ the Doppler effect to assess whether structures (usually blood) are moving towards or away from the probe, and its relative velocity. By calculating the frequency shift of a particular sample volume, for example flow in an artery or a jet of blood flow over a heart valve, its speed and direction can be determined and visualised. This is particularly useful in cardiovascular studies (sonography of the vascular system and heart) and essential in many areas such as determining reverse blood flow in the liver vasculature in portal hypertension. The Doppler information is displayed graphically using spectral Doppler, or as an image using color Doppler (directional Doppler) or power Doppler (non directional Doppler). This Doppler shift falls in the audible range and is often presented audibly using stereo speakers: this produces a very distinctive, although synthetic, pulsating sound.

Most modern sonographic machines use pulsed Doppler to measure velocity. Pulsed wave machines transmit and receive series of pulses. The frequency shift of each pulse is ignored, however the relative phase changes of the pulses are used to obtain the frequency shift (since frequency is the rate of change of phase). The major advantages of pulsed Doppler over continuous wave is that distance information is obtained (the time between the transmitted and received pulses can be converted into a distance with knowledge of the speed of sound) and gain correction is applied. The disadvantage of pulsed Doppler is that the measurements can suffer from aliasing. The terminology "Doppler ultrasound" or "Doppler sonography", has been accepted to apply to both pulsed and continuous Doppler systems despite the different mechanisms by which the velocity is measured.

It should be noted here that there are no standards for the display of color Doppler. Some laboratories insist on showing arteries as red and veins as blue, as medical illustrators usually show them, even though, as a result, a tortuous vessel may have portions with flow toward and away relative to the transducer. This can result in the illogical appearance of blood flow that appears to be in both directions in the same vessel. Other laboratories use red to indicate flow toward the transducer and blue away from the transducer which is the reverse of 150 years of astronomical literature on the Doppler effect. Still other laboratories prefer to display the sonographic Doppler color map more in accord with the prior published physics with the red shift representing longer waves of echoes (scattered) from blood flowing away from the transducer; and with blue representing the shorter waves of echoes reflecting from blood flowing toward the transducer. Because of this confusion and lack of standards in the various laboratories, the sonographer must understand the underlying acoustic physics of color Doppler and the physiology of normal and abnormal blood flow in the human body.^{[9] [10] [11] [12]}



Spectral Doppler of Common Carotid Artery



Colour Doppler of Common Carotid Artery



Computer-enhanced transcranial doppler.

Contrast media

The use of microbubble contrast media in medical sonography to improve ultrasound signal backscatter is known as contrast-enhanced ultrasound. This technique is currently used in echocardiography, and may have future applications in molecular imaging and drug delivery.

Compression ultrasonography

Compression ultrasonography is a technique used for diagnosing deep vein thrombosis and combines ultrasonography of the deep veins with venous compression.^[13] The technique can be used on deep veins of the upper and lower extremities, with some laboratories limiting the examination to the common femoral vein and the popliteal vein, whereas other laboratories examine the deep veins from the inguinal region to the calf, including the calf veins.^[13]

Compression ultrasonography in B-mode has both high sensitivity and specificity for detecting proximal deep vein thrombosis in symptomatic patients. The sensitivity lies somewhere between 90 to 100% for the diagnosis of symptomatic deep vein thrombosis, and the specificity ranges between 95 to 100%.^[13]

Attributes

As with all imaging modalities, ultrasonography has its list of positive and negative attributes.

Strengths

- It images muscle, soft tissue, and bone surfaces very well and is particularly useful for delineating the interfaces between solid and fluid-filled spaces.
- It renders "live" images, where the operator can dynamically select the most useful section for diagnosing and documenting changes, often enabling rapid diagnoses. Live images also allow for ultrasound-guided biopsies or injections, which can be cumbersome with other imaging modalities.
- It shows the structure of organs.
- It has no known long-term side effects and rarely causes any discomfort to the patient.
- Equipment is widely available and comparatively flexible.
- Small, easily carried scanners are available; examinations can be performed at the bedside.
- Relatively inexpensive compared to other modes of investigation, such as computed X-ray tomography, DEXA or magnetic resonance imaging.
- Spatial resolution is better in high frequency ultrasound transducers than it is in most other imaging modalities.
- Through the use of an Ultrasound research interface, an ultrasound device can offer a relatively inexpensive, real-time, and flexible method for capturing data required for special research purposes for tissue characterization and development of new image processing techniques

Weaknesses

- Sonographic devices have trouble penetrating bone. For example, sonography of the adult brain is very limited though improvements are being made in transcranial ultrasonography.
- Sonography performs very poorly when there is a gas between the transducer and the organ of interest, due to the extreme differences in acoustic impedance. For example, overlying gas in the gastrointestinal tract often makes ultrasound scanning of the pancreas difficult, and lung imaging is not possible (apart from demarcating pleural effusions).
- Even in the absence of bone or air, the depth penetration of ultrasound may be limited depending on the frequency of imaging. Consequently, there might be difficulties imaging structures deep in the body, especially in obese patients.

- Body habitus has a large influence on image quality, image quality and accuracy of diagnosis is limited with obese patients, overlying subcutaneous fat attenuates the sound beam and a lower frequency transducer is required (with lower resolution)

The method is operator-dependent. A high level of skill and experience is needed to acquire good-quality images and make accurate diagnoses.

- There is no scout image as there is with CT and MRI. Once an image has been acquired there is no exact way to tell which part of the body was imaged.

Risks and side-effects

Ultrasonography is generally considered a "safe" imaging modality.^[14] However slight detrimental effects have been occasionally observed (see below). Diagnostic ultrasound studies of the foetus are generally considered to be safe during pregnancy. This diagnostic procedure should be performed only when there is a valid medical indication, and the lowest possible ultrasonic exposure setting should be used to gain the necessary diagnostic information under the "as low as reasonably achievable" or ALARA principle.

World Health Organizations technical report series 875(1998).^[15] supports that ultrasound is harmless: "Diagnostic ultrasound is recognized as a safe, effective, and highly flexible imaging modality capable of providing clinically relevant information about most parts of the body in a rapid and cost-effective fashion". Although there is no evidence ultrasound could be harmful for the foetus, US Food and Drug Administration views promotion, selling, or leasing of ultrasound equipment for making "keepsake foetal videos" to be an unapproved use of a medical device.

Studies on the safety of ultrasound

- A study at the Yale School of Medicine found a correlation between prolonged and frequent use of ultrasound and abnormal neuronal migration in mice.^[16] A meta-analysis of several ultrasonography studies found no statistically significant harmful effects from ultrasonography, but mentioned that there was a lack of data on long-term substantive outcomes such as neurodevelopment.^[17]

Regulation

Diagnostic and therapeutic ultrasound equipment is regulated in the USA by the FDA, and worldwide by other national regulatory agencies. The FDA limits acoustic output using several metrics. Generally other regulatory agencies around the world accept the FDA-established guidelines.

Currently New Mexico is the only state in the USA which regulates diagnostic medical sonographers. Certification examinations for sonographers are available in the US from three organizations: The American Registry of Diagnostic Medical Sonography^[18], Cardiovascular Credentialing International^[19] and the American Registry of Radiological Technologists^[20].

The primary regulated metrics are MI (Mechanical Index) a metric associated with the cavitation bio-effect, and TI (Thermal Index) a metric associated with the tissue heating bio-effect. The FDA requires that the machine not exceed limits that they have established. This requires self-regulation on the part of the manufacturer in terms of the calibration of the machine. The established limits are reasonably conservative so as to maintain diagnostic ultrasound as a safe imaging modality.^[21]

In India, lack of social security and consequent preference for a male child has popularized the use of ultrasound technology to identify and abort female fetuses. India's Pre-natal Diagnostic Techniques act makes use of ultrasound for sex selection illegal,^[22] but unscrupulous Indian doctors and would-be parents continue to discriminate against the girl child.

Career Information

According to the Society of Diagnostic Medical Sonography ^[23], a diagnostic medical sonographer in the United States of America earns an average of \$66,768 (2008). Sonographers work in a variety of settings including hospitals, clinics, physician offices, and mobile labs. Some even use their skills and knowledge in veterinary offices. Information ^[24] about a career in Diagnostic Medical Sonography is available from the Society of Diagnostic Medical Sonography. The US Department of Labor also provides information about the field in its Occupation Outlook Handbook ^[25].

History

United States

Ultrasonic energy was first applied to the human body for medical purposes by Dr. George Ludwig at the Naval Medical Research Institute, Bethesda, Maryland in the late 1940s.^[26] ^[27] English born and educated John Wild (1914–2009) first used ultrasound to assess the thickness of bowel tissue as early as 1949: for his early work he has been described as the "father of medical ultrasound".^[28]

In 1962, after about two years of work, Joseph Holmes, William Wright, and Ralph Meyerdirk developed the first compound contact B-mode scanner. Their work had been supported by U.S. Public Health Services and the University of Colorado. Wright and Meyerdirk left the University to form Physionic Engineering Inc., which launched the first commercial hand-held articulated arm compound contact B-mode scanner in 1963. This was the start of the most popular design in the history of ultrasound scanners.^[29]

The first demonstration of color Doppler was by Geoff Stevenson, who was involved in the early developments and medical use of Doppler shifted ultrasonic energy.^[30]

Sweden

Medical ultrasonography was used 1953 at Lund University by cardiologist Inge Edler and Carl Hellmuth Hertz, the son of Gustav Ludwig Hertz, who was a graduate student at the department of nuclear physics.

Edler had asked Hertz if it was possible to use radar to look into the body, but Hertz said this was impossible. However, he said, it might be possible to use ultrasonography. Hertz was familiar with using ultrasonic reflectoscopes for nondestructive materials testing, and together they developed the idea of using this method in medicine.

The first successful measurement of heart activity was made on October 29, 1953 using a device borrowed from the ship construction company Kockums in Malmö. On December 16 the same year, the method was used to generate an echo-encephalogram (ultrasonic probe of the brain). Edler and Hertz published their findings in 1954.^[31]

Scotland

Parallel developments in Glasgow, Scotland by Professor Ian Donald and colleagues at the Glasgow Royal Maternity Hospital (GRMH) led to the first diagnostic applications of the technique. Donald was an obstetrician with a self-confessed "childish interest in machines, electronic and otherwise", who, having treated the wife of one of the company's directors, was invited to visit the Research Department of boilermakers Babcock & Wilcox at Renfrew, where he used their industrial ultrasound equipment to conduct experiments on various morbid anatomical specimens and assess their ultrasonic characteristics. Together with the medical physicist Tom Brown and fellow obstetrician Dr John MacVicar, Donald refined the equipment to enable differentiation of pathology in live volunteer patients. These findings were reported in *The Lancet* on 7 June 1958^[32] as "Investigation of Abdominal Masses by Pulsed Ultrasound" - possibly one of the most important papers ever published in the field of diagnostic medical imaging.

At GRMH, Professor Donald and Dr James Willocks then refined their techniques to obstetric applications including foetal head measurement to assess the size and growth of the foetus. With the opening of the new Queen Mother's Hospital in Yorkhill in 1964, it became possible to improve these methods even further. Dr Stuart Campbell's pioneering work on foetal cephalometry led to it acquiring long-term status as the definitive method of study of foetal growth. As the technical quality of the scans was further developed, it soon became possible to study pregnancy from start to finish and diagnose its many complications such as multiple pregnancy, foetal abnormality and *placenta praevia*. Diagnostic ultrasound has since been imported into practically every other area of medicine.

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External links

- American Institute of Ultrasound in Medicine (<http://www.aium.org>) Professional Association
- About the discovery of medical ultrasonography (<http://www.ob-ultrasound.net/ingehertz.html>)
- History of medical sonography (ultrasound) (<http://www.ob-ultrasound.net/history1.html>)
- Procedures in Ultrasound (Sonography) (<http://radiologyinfo.org/en/sitemap/modal-alias.cfm?modal=US>) for patients, from RadiologyInfo.org
- The Global Library of Women's Medicine (<http://www.glowm.com/?p=glowm.cml/homelinks&linkid=101>) Imaging in Obstetrics and Gynecology Link. Non-profit offering freely downloadable expert material for healthcare professionals.
- Careers in the vascular ultrasound field (<http://www.svunet.org/i4a/pages/index.cfm?pageid=3322>)
- Sonography of the female pelvic floor:clinical indications and techniques (http://www.pelvipervineology.org/practical/sonography_female_pelvic_floor_clinical_indications_and_techniques.html) Illustrate the clinical utility of this non-invasive diagnostic technique.
- How to Become an Ultrasound Technician - a wiki article on becoming an ultrasound technician.
- A Pilot Study of Comprehensive Ultrasound Education at the Wayne State University School of Medicine: <http://www.jultrasoundmed.org/cgi/content/abstract/27/5/745?ck=nck>

Optical imaging

Optical imaging is an imaging technique.

Optics usually describes the behavior of visible, ultraviolet, and infrared light used in imaging.

Because light is an electromagnetic wave, similar phenomena occur in X-rays, microwaves, radio waves. Chemical imaging or molecular imaging ^[1] ^[2] ^[3] involves inference from the deflection of light emitted from (e.g. laser, infrared) source to structure, texture, anatomic and chemical properties of material (e.g. crystal, cell tissue). Optical imaging systems may be divided into diffusive ^[4] and ballistic imaging ^[5] systems.

Diffusive optical imaging in neuroscience

Diffusive optical imaging (also known as *Near Infrared Optical Tomography* or NIROT) is a technique that gives neuroscientists the ability to simultaneously obtain information about the source of neural activity as well as its time course. In other words, it allows them to "see" neural activity and study the functioning of the brain.

In this method, a near-infrared laser is positioned on the scalp. Detectors composed of optical fiber bundles are located a few centimeters away from the light source. These detectors sense how the path of light is altered, either through absorption or scattering, as it traverses brain tissue.

This method can provide two types of information. First, it can be used to measure the absorption of light, which is related to concentration of chemicals in the brain. Second, it can measure the scattering of light, which is related to physiological characteristics such as the swelling of glia and neurons that are associated with neuronal firing.

Typical applications include rapid 2D optical *topographic* imaging of the event-related optical signal (EROS) or Near infrared spectroscopy (NIRS) signal following brain activity and *tomographic* reconstruction of an entire 3D volume of tissue to diagnose breast cancer or neonatal brain haemorrhage. The spatial resolution of DOT techniques

is several millimeters, comparable to the lower end of functional magnetic resonance imaging (fMRI). The temporal resolution of EROS is very good, comparable to electroencephalography, and magnetoencephalography (~milliseconds), while that of NIRS, which measures hemodynamic changes rather than neuronal activity, is comparable to fMRI (~seconds). DOT instruments are relatively low cost (\$150,000), portable and immune to electrical interference. The signal-to-noise ratio of NIRS is quite good, enabling detection of responses to single events in many cases. EROS signals are much weaker, typically requiring averaging of many responses.

Important chemicals that this method can detect include hemoglobin and cytochromes.

Ballistic optical imaging

Ballistic optical imaging systems ignore the diffused photons and rely only on the ballistic photons to create high-resolution (near diffraction limited) images through scattering media.

See also

- Photon diffusion
- Ballistic imaging
- Photon diffusion equation

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External links

- Understanding Near-Infrared Imaging (http://www.licor.com/bio/products/imaging_systems/pearl/pearl_sensitivity.jsp/) – Resource to better understand the benefits of Near-Infrared imaging.
- Diffuse Optics Lab at University of Pennsylvania, Philadelphia (<http://www.lrsu.upenn.edu/pmi>)
- DOI at Massachusetts General Hospital, Boston (<http://www.nmr.mgh.harvard.edu/martinos/research/technologiesDOI.php>)
- Biomedical Imaging Group at Dartmouth (<http://www-nml.dartmouth.edu/biomedprg/biomed.html>)
- DOS/I Lab at the Beckman Laser Institute, University of California, Irvine (<http://dosi.bli.uci.edu>)
- A review article in the field by A.P. Gibson et al. (<http://www.iop.org/EJ/abstract/0031-9155/50/4/R01>)
- An article on optical breast imaging (<http://medicalphysicsweb.org/cws/article/research/27299>)
- Illinois ECE 460 Principles of Optical Imaging (<http://nanohub.org/resources/5163>) Course lecture notes

Fluorescence microscope

A **fluorescence microscope** (colloquially synonymous with *epifluorescence microscope*) is an optical microscope used to study properties of organic or inorganic substances using the phenomena of fluorescence and phosphorescence instead of, or in addition to, reflection and absorption.^{[1] [2]}

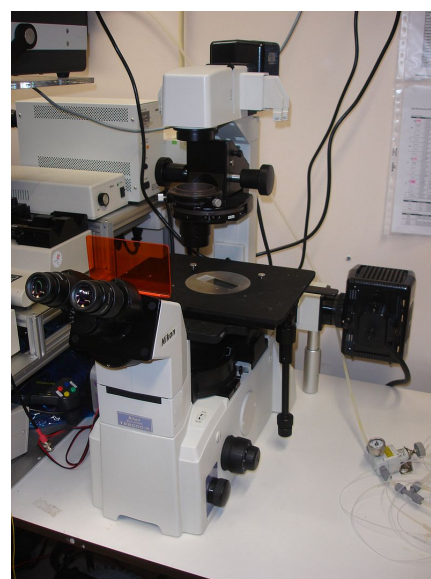


An upright fluorescence microscope (Olympus BX61) with the fluorescent filter cube turret above the objective lenses, coupled with a digital camera.

Technique

In most cases, a component of interest in the specimen can be labeled specifically with a fluorescent molecule called a fluorophore (such as green fluorescent protein (GFP), fluorescein or DyLight 488).^[1] The specimen is illuminated with light of a specific wavelength (or wavelengths) which is absorbed by the fluorophores, causing them to emit light of longer wavelengths (i.e. of a different color than the absorbed light). The illumination light is separated from the much weaker emitted fluorescence through the use of a spectral emission filter. Typical components of a fluorescence microscope are the light source (xenon arc lamp or mercury-vapor lamp), the excitation filter, the dichroic mirror (or dichromatic beamsplitter), and the emission filter (see figure below). The filters and the dichroic are chosen to match the spectral excitation and emission characteristics of the fluorophore used to label the specimen.^[1] In this manner, the distribution of a single fluorophore (color) is imaged at a time. Multi-color images of several types of fluorophores must be composed by combining several single-color images.^[1]

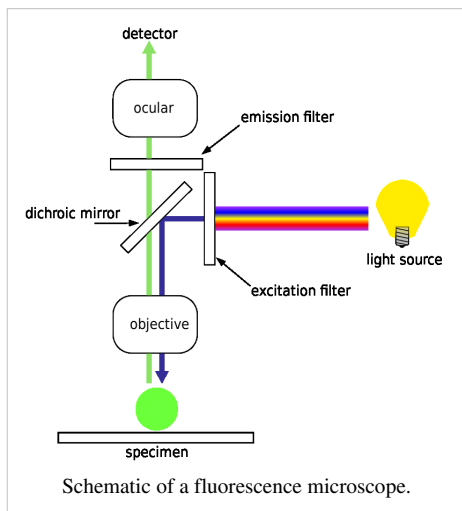
Most fluorescence microscopes in use are epifluorescence microscopes (i.e. excitation and observation of the fluorescence are from above (*epi*–) the specimen). These microscopes have become an important part in the field of biology, opening the doors for more advanced microscope designs, such as the confocal microscope and the total internal reflection fluorescence microscope (TIRF).



An inverted fluorescence microscope (Nikon TE2000) with the fluorescent filter cube turret below the stage. Note the orange plate that allows the user to look at a sample while protecting their eyes from the UV light.

Fluorophores lose their ability to fluoresce as they are illuminated in a process called photobleaching. Special care must be taken to prevent photobleaching through the use of more robust fluorophores, by minimizing illumination, or by introducing a scavenger system to reduce the rate of photobleaching.

Epifluorescence microscopy



Epifluorescence microscopy is a method of fluorescence microscopy that is widely used in life sciences. The excitatory light is passed from above (or, for inverted microscopes, from below), through the objective lens and then onto the specimen instead of passing it first through the specimen. The fluorescence in the specimen gives rise to emitted light which is focused to the detector by the same objective that is used for the excitation. Since most of the excitatory light is transmitted through the specimen, only reflected excitatory light reaches the objective together with the emitted light and this method therefore gives an improved signal to noise ratio. An additional filter between the objective and the detector can filter out the remaining excitation light from fluorescent light. A common use in biology is to apply fluorescent or fluorochrome stains to the specimen in order to image distributions of proteins or other molecules of interest.

Improvements and sub-diffraction techniques

The nature of light limits the size of the spot to which light can be focused. According to the diffraction limit a focused light distribution cannot be made smaller than approximately half of the wavelength of the used light. Uncovered in the 19th century by Ernst Abbe this has been a barrier of the achievable resolution of fluorescence light microscopes for a long time. While resolution is denoted by the ability to discern different objects of the same kind, localizing or tracking of single particles have been performed with a precision much below the diffraction limit.

Several improvements in microscopy techniques have been invented in the 20th century and have resulted in increased resolution and contrast to some extent. However they did not overcome the diffraction limit. In 1978 first theoretical ideas have been developed to break this barrier by using a 4Pi microscope as a confocal laser scanning fluorescence microscope where the light is focused ideally from all sides to a common focus which is used to scan the object by 'point-by-point' excitation combined with 'point-by-point' detection^[3]. However, the first experimental demonstration of the 4pi microscope took place in 1994^[4]. The 4Pi microscopy is maximizing the amount of available focusing directions by using two opposing objective lenses or Multi-photon microscopy using redshifted light and multi-photon excitation.

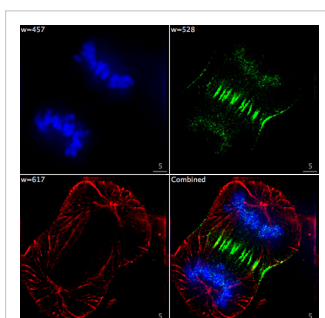
The first technique to really achieve a sub-diffraction resolution was STED microscopy, proposed in 1994. This method and all techniques following the RESOLFT concept rely on a strong non-linear interaction between light and fluorescing molecules. The molecules are driven strongly between distinguishable molecular states at each specific location, so that finally light can be emitted at only a small fraction of space, hence an increased resolution.

As well in the 1990s another super resolution microscopy method based on wide field microscopy has been developed. Substantially improved size resolution of cellular nanostructures stained with a fluorescent marker was achieved by development of SPDM localization microscopy and the structured laser illumination (spatially modulated illumination, SMI)^[5]. Combining the principle of SPDM with SMI resulted in the development of the Vertico SMI microscope^{[6] [7]}. Single molecule detection of normal blinking fluorescent dyes like GFP can be achieved by using a further development of SPDM the so-called SPDMphymod technology which makes it possible

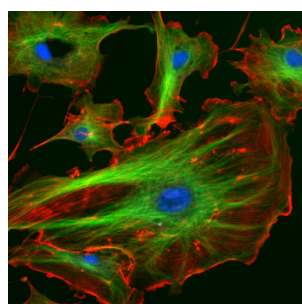
to detect and count two different fluorescent molecule types at the molecular level (this technology is referred to as 2CLM, 2 Color Localization Microscopy) ^[8].

Alternatively, the advent of photoactivated localization microscopy could achieve similar results by relying on blinking or switching of single molecules, where the fraction of fluorescing molecules is very small at each time. This stochastic response of molecules on the applied light corresponds also to a highly nonlinear interaction, leading to subdiffraction resolution.

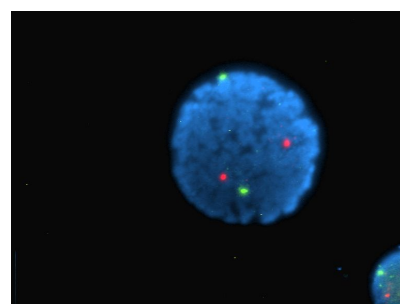
Gallery



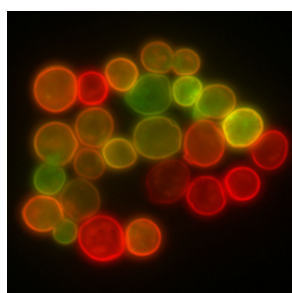
Epifluorescent imaging of the three components in a dividing human cancer cell. DNA is stained blue, a protein called INCENP is green, and the microtubules are red. Each fluorophore is imaged separately using a different combination of excitation and emission filters, and the images are captured sequentially using a digital CCD camera, then overlaid to give a complete image.



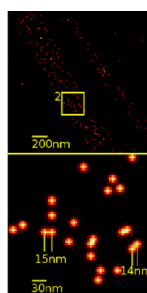
Endothelial cells under the microscope. Nuclei are stained blue with DAPI, microtubules are marked green by an antibody bound to FITC and actin filaments are labeled red with phalloidin bound to TRITC. Bovine pulmonary artery endothelial (BPAE) cells



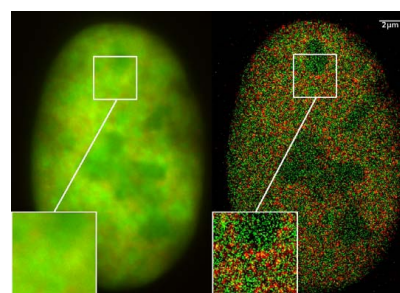
Human lymphocyte nucleus stained with DAPI with chromosome 13 (green) and 21 (red) centromere probes hybridized (Fluorescent in situ hybridization (FISH))



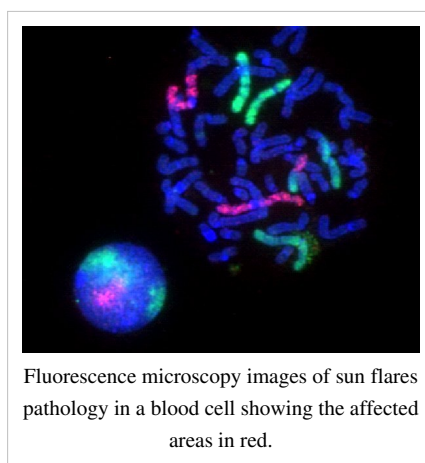
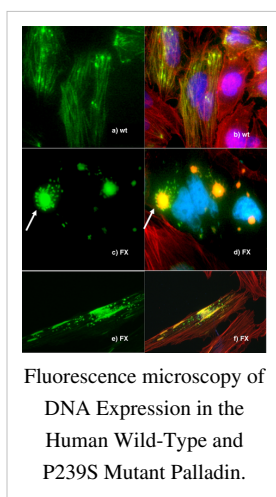
Yeast cell membrane visualized by some membrane proteins fused with RFP and GFP fluorescent markers. Imposition of light from both of markers results in yellow color.



Super Resolution Microscopy: Single YFP molecule detection in a human cancer cell. Typical distance measurements in the 15 nm range (5 nm standard deviation) measured with a Vertico-SMI/SPDMphymod microscope



Super Resolution Microscopy: Co-localization microscopy (2CLM) with GFP and RFP fusion proteins (nucleus of a bone cancer cell) 120.000 localized molecules in a wide-field area ($470 \mu\text{m}^2$) measured with a Vertico-SMI/SPDMphymod microscope



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FNIR

fNIR stands for **functional near-infrared imaging**. fNIR is a spectroscopic neuro-imaging method for measuring the level of neuronal activity in the brain. The method is based on neuro-vascular coupling, that is, the relationship between metabolic activity and oxygen level (oxygenated hemoglobin) in feeding blood vessels.

There are three types of fNIR:

- CW - continuous wave - In this method, infrared light shines at the same intensity level during the measurement period. The detected signal is lower intensity static signal (dc valued)
- FD - frequency domain - In this method, input signal is modulated sinusoid at some frequency and detected output signal has changes in amplitude and phase.
- TR - time resolved - In time resolve spectroscopy, a very short pulse is introduced to measured and the pulse length is usually on the order of picoseconds. The detected signal is usually a longer signal and has a decay time.
- fNIR device was first invented by Dr. Britton Chance of the University of Pennsylvania. Current cwFNIR devices have improved with the advent of electronics.[1] At the Optical Brain Imaging Lab of Drexel University, in collaboration with Penn, battery operated, wireless cwfNIR devices have been developed.[2]

External links

- Lab of BC at University of Pennsylvania ^[3]
- Optical Brain Imaging Lab at Drexel University ^[4]

See also

- Near infrared spectroscopy
- Optical imaging

References

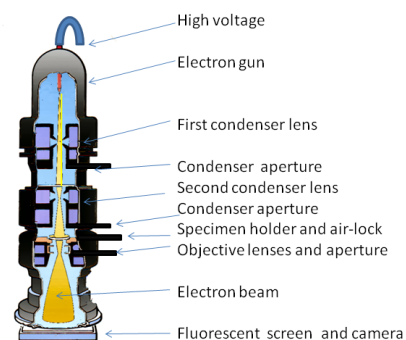
- [1] http://www.redorbit.com/news/health/107194/athome_breast_cancer_detector_tested/index.html
 - [2] <http://www.newswise.com/articles/view/518934/>
 - [3] <http://www.uphs.upenn.edu/biobiop/faculty/pages/chance.html>
 - [4] <http://www.biomed.drexel.edu/fnir/>
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Electron microscope

An **electron microscope** is a type of microscope that produces an electronically-magnified image of a specimen for detailed observation. The electron microscope (EM) uses a particle beam of electrons to illuminate the specimen and create a magnified image of it. The microscope has a greater resolving power than a light-powered optical microscope, because it uses electrons that have wavelengths about 100,000 times shorter than visible light (photons), and can achieve magnifications of up to 2,000,000x, whereas ordinary, non-confocal light microscopes are limited to 2000x magnification.

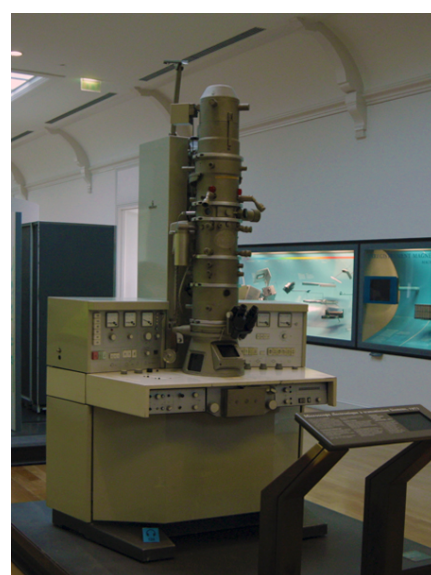
The electron microscope uses electrostatic and electromagnetic "lenses" to control the electron beam and focus it to form an image. These lenses are analogous to, but different from the glass lenses of an optical microscope that form a magnified image by focusing light on or through the specimen. In transmission, the electron beam is first diffracted by the specimen, and then, the electron microscope "lenses" re-focus the beam into a Fourier-transformed image of the diffraction pattern for the selected area of investigation. The real image thus formed is a highly 'magnified' image by a factor of several million, and can be then recorded on a special photographic plate, or viewed on a detecting screen. Electron microscopes are used to observe a wide range of biological and inorganic specimens including microorganisms, cells, large molecules, biopsy samples, metals, and crystals. Industrially, the electron microscope is primarily used for quality control and failure analysis in semiconductor device fabrication.

An electron microscope's advantages over X-ray crystallography are that the specimen need not be a single crystal or even a polycrystalline powder, and also that the Fourier transform reconstruction of the object's magnified structure occurs physically and thus avoids the need for solving the phase problem faced by the X-ray crystallographers after obtaining their X-ray diffraction patterns of a single crystal or polycrystalline powder. The transmission electron microscope's major 'disadvantage' is the need for extremely thin sections of the specimens, typically less than 10 nanometers. For biological specimens it also requires biological sample special 'staining' with heavy atom labels in order to achieve the required contrast, and then chemical fixation as well as encasing with a polymer resin to stabilize the biological specimen which is thin sectioned.



Transmission Electron Microscope

Diagram of a transmission electron microscope



A 1973 Siemens electron microscope, Musée des Arts et Métiers, Paris

History

In 1931, the German physicist Ernst Ruska and German electrical engineer Max Knoll constructed the prototype electron microscope, capable of four-hundred-power magnification; the apparatus was a practical application of the principles of electron microscopy.^[1] Two years later, in 1933, Ruska built an electron microscope that exceeded the resolution attainable with an optical (lens) microscope.^[1] Moreover, Reinhold Rudenberg, the scientific director of Siemens-Schuckertwerke, obtained the patent for the electron microscope in May 1931. Family illness compelled the electrical engineer to devise an electrostatic microscope, because he wanted to make visible the poliomyelitis virus.

In 1937, the Siemens company financed the development work of Ernst Ruska and Bodo von Borries, and employed Helmut Ruska (Ernst's brother) to develop applications for the microscope, especially with biologic specimens.^[1] ^[2] Also in 1937, Manfred von Ardenne pioneered the scanning electron microscope.^[3] The first *practical* electron microscope was constructed in 1938, at the University of Toronto, by Eli Franklin Burton and students Cecil Hall, James Hillier, and Albert Prebus; and Siemens produced the first *commercial* Transmission Electron Microscope (TEM) in 1939.^[4] Although contemporary electron microscopes are capable of two million-power magnification, as scientific instruments, they remain based upon Ruska's prototype.



Electron microscope constructed by Ernst Ruska in 1933

Types

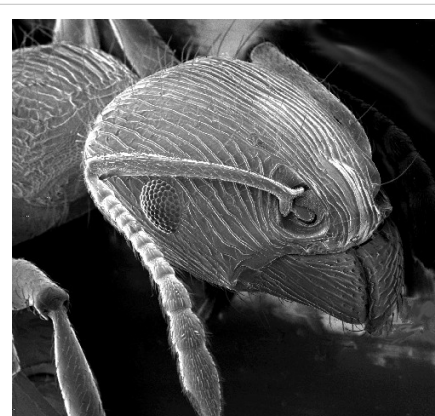
Transmission electron microscope (TEM)

The original form of electron microscope, the transmission electron microscope (TEM) uses a high voltage electron beam to create an image. The electrons are emitted by an electron gun, commonly fitted with a tungsten filament cathode as the electron source. The electron beam is accelerated by an anode typically at +100 keV (40 to 400 keV) with respect to the cathode, focused by electrostatic and electromagnetic lenses, and transmitted through the specimen that is in part transparent to electrons and in part scatters them out of the beam. When it emerges from the specimen, the electron beam carries information about the structure of the specimen that is magnified by the objective lens system of the microscope. The spatial variation in this information (the "image") is viewed by projecting the magnified electron image onto a fluorescent viewing screen coated with a phosphor or scintillator material such as zinc sulfide. The image can be photographically recorded by exposing a photographic film or plate directly to the electron beam, or a high-resolution phosphor may be coupled by means of a lens optical system or a fibre optic light-guide to the sensor of a CCD (charge-coupled device) camera. The image detected by the CCD may be displayed on a monitor or computer.

Resolution of the TEM is limited primarily by spherical aberration, but a new generation of aberration correctors have been able to partially overcome spherical aberration to increase resolution. Hardware correction of spherical aberration for the High Resolution TEM (HRTEM) has allowed the production of images with resolution below 0.5 Ångström (50 picometres)^[5] at magnifications above 50 million times.^[6] The ability to determine the positions of atoms within materials has made the HRTEM an important tool for nano-technologies research and development.^[7]

Scanning electron microscope (SEM)

Unlike the TEM, where electrons of the high voltage beam carry the image of the specimen, the electron beam of the Scanning Electron Microscope (SEM)^[8] does not at any time carry a complete image of the specimen. The SEM produces images by probing the specimen with a focused electron beam that is scanned across a rectangular area of the specimen (raster scanning). At each point on the specimen the incident electron beam loses some energy, and that lost energy is converted into other forms, such as heat, emission of low-energy secondary electrons, light emission (cathodoluminescence) or x-ray emission. The display of the SEM maps the varying intensity of any of these signals into the image in a position corresponding to the position of the beam on the specimen when the signal was generated. In the SEM image of an ant shown at right, the image was constructed from signals produced by a secondary electron detector, the normal or conventional imaging mode in most SEMs.



An image of an ant in a scanning electron microscope

Generally, the image resolution of an SEM is about an order of magnitude poorer than that of a TEM. However, because the SEM image relies on surface processes rather than transmission, it is able to image bulk samples up to many centimetres in size and (depending on instrument design and settings) has a great depth of field, and so can produce images that are good representations of the three-dimensional shape of the sample.

Reflection electron microscope (REM)

In the **Reflection Electron Microscope (REM)** as in the TEM, an electron beam is incident on a surface, but instead of using the transmission (TEM) or secondary electrons (SEM), the reflected beam of elastically scattered electrons is detected. This technique is typically coupled with Reflection High Energy Electron Diffraction (RHEED) and *Reflection high-energy loss spectrum (RHELS)*. Another variation is Spin-Polarized Low-Energy Electron Microscopy (SPLEEM), which is used for looking at the microstructure of magnetic domains.^[9]

Scanning transmission electron microscope (STEM)

The STEM rasters a focused incident probe across a specimen that (as with the TEM) has been thinned to facilitate detection of electrons scattered *through* the specimen. The high resolution of the TEM is thus possible in STEM. The focusing action (and aberrations) occur before the electrons hit the specimen in the STEM, but afterward in the TEM. The STEMs use of SEM-like beam rastering simplifies annular dark-field imaging, and other analytical techniques, but also means that image data is acquired in serial rather than in parallel fashion.

Low voltage electron microscope (LVEM)

The low voltage electron microscope (LVEM) is a combination of SEM, TEM and STEM in one instrument, which operates at relatively low electron accelerating voltage of 5 kV. Low voltage increases image contrast which is especially important for biological specimens. This increase in contrast significantly reduces, or even eliminates the need to stain. Sectioned samples generally need to be thinner than they would be for conventional TEM (20-65 nm). Resolutions of a few nm are possible in TEM, SEM and STEM modes.^{[10] [11]}

Sample preparation

Materials to be viewed under an electron microscope may require processing to produce a suitable sample. The technique required varies depending on the specimen and the analysis required:

- *Chemical fixation* for biological specimens aims to stabilize the specimen's mobile macromolecular structure by chemical crosslinking of proteins with aldehydes such as formaldehyde and glutaraldehyde, and lipids with osmium tetroxide.
- *Cryofixation* – freezing a specimen so rapidly, to liquid nitrogen or even liquid helium temperatures, that the water forms vitreous (non-crystalline) ice. This preserves the specimen in a snapshot of its solution state. An entire field called cryo-electron microscopy has branched from this technique. With the development of cryo-electron microscopy of vitreous sections (CEMOVIS), it is now possible to observe samples from virtually any biological specimen close to its native state.
- *Dehydration* – freeze drying, or replacement of water with organic solvents such as ethanol or acetone, followed by critical point drying or infiltration with embedding resins.
- *Embedding, biological specimens* – after dehydration, tissue for observation in the transmission electron microscope is embedded so it can be sectioned ready for viewing. To do this the tissue is passed through a 'transition solvent' such as epoxy propane and then infiltrated with a resin such as Araldite epoxy resin; tissues may also be embedded directly in water-miscible acrylic resin. After the resin has been polymerised (hardened) the sample is thin sectioned (ultrathin sections) and stained - it is then ready for viewing.
- *Embedding, materials* - after embedding in resin, the specimen is usually ground and polished to a mirror-like finish using ultra-fine abrasives. The polishing process must be performed carefully to minimize scratches and other polishing artifacts that reduce image quality.
- *Sectioning* – produces thin slices of specimen, semitransparent to electrons. These can be cut on an ultramicrotome with a diamond knife to produce ultrathin slices about 60-90 nm thick. Disposable glass knives are also used because they can be made in the lab and are much cheaper.
- *Staining* – uses heavy metals such as lead, uranium or tungsten to scatter imaging electrons and thus give contrast between different structures, since many (especially biological) materials are nearly "transparent" to electrons (weak phase objects). In biology, specimens can be stained "en bloc" before embedding and also later after sectioning. Typically thin sections are stained for several minutes with an aqueous or alcoholic solution of uranyl acetate followed by aqueous lead citrate.
- *Freeze-fracture or freeze-etch* – a preparation method particularly useful for examining lipid membranes and their incorporated proteins in "face on" view. The fresh tissue or cell suspension is frozen rapidly (cryofixed), then fractured by simply breaking or by using a microtome while maintained at liquid nitrogen temperature. The cold fractured surface (sometimes "etched" by increasing the temperature to about $-100\text{ }^{\circ}\text{C}$ for several minutes to let some ice sublime) is then shadowed with evaporated platinum or gold at an average angle of 45° in a high vacuum evaporator. A second coat of carbon, evaporated perpendicular to the average surface plane is often performed to improve stability of the replica coating. The specimen is returned to room temperature and pressure, then the extremely fragile "pre-shadowed" metal replica of the fracture surface is released from the underlying biological material by careful chemical digestion with acids, hypochlorite solution or SDS detergent. The still-floating replica is thoroughly washed from residual chemicals, carefully fished up on fine grids, dried then viewed in the TEM.



An insect coated in gold for viewing with a scanning electron microscope.

- *Ion Beam Milling* – thins samples until they are transparent to electrons by firing ions (typically argon) at the surface from an angle and sputtering material from the surface. A subclass of this is Focused ion beam milling, where gallium ions are used to produce an electron transparent membrane in a specific region of the sample, for example through a device within a microprocessor. Ion beam milling may also be used for cross-section polishing prior to SEM analysis of materials that are difficult to prepare using mechanical polishing.
- *Conductive Coating* – an ultrathin coating of electrically-conducting material, deposited either by high vacuum evaporation or by low vacuum sputter coating of the sample. This is done to prevent the accumulation of static electric fields at the specimen due to the electron irradiation required during imaging. Such coatings include gold, gold/palladium, platinum, tungsten, graphite etc. and are especially important for the study of specimens with the scanning electron microscope. Another reason for coating, even when there is more than enough conductivity, is to improve contrast, a situation more common with the operation of a FESEM (field emission SEM).

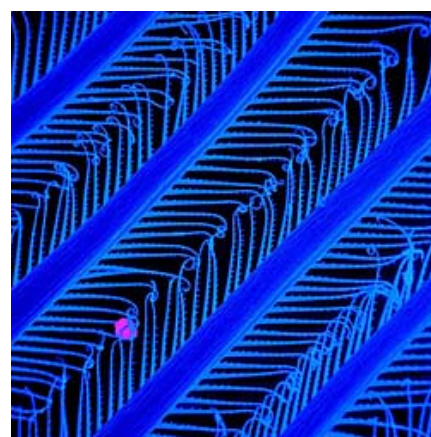
Disadvantages

Electron microscopes are expensive to build and maintain, but the capital and running costs of confocal light microscope systems now overlaps with those of basic electron microscopes. They are dynamic rather than static in their operation, requiring extremely stable high-voltage supplies, extremely stable currents to each electromagnetic coil/lens, continuously-pumped high- or ultra-high-vacuum systems, and a cooling water supply circulation through the lenses and pumps. As they are very sensitive to vibration and external magnetic fields, microscopes designed to achieve high resolutions must be housed in stable buildings (sometimes underground) with special services such as magnetic field cancelling systems. Some desktop low voltage electron microscopes have TEM capabilities at very low voltages (around 5 kV) without stringent voltage supply, lens coil current, cooling water or vibration isolation requirements and as such are much less expensive to buy and far easier to install and maintain, but do not have the same ultra-high (atomic scale) resolution capabilities as the larger instruments.

The samples largely have to be viewed in vacuum, as the molecules that make up air would scatter the electrons. One exception is the environmental scanning electron microscope, which allows hydrated samples to be viewed in a low-pressure (up to 20 Torr/2.7 kPa), wet environment.

Scanning electron microscopes usually image conductive or semi-conductive materials best. Non-conductive materials can be imaged by an environmental scanning electron microscope. A common preparation technique is to coat the sample with a several-nanometer layer of conductive material, such as gold, from a sputtering machine; however, this process has the potential to disturb delicate samples.

Small, stable specimens such as carbon nanotubes, diatom frustules and small mineral crystals (asbestos fibres, for example) require no special treatment before being examined in the electron microscope. Samples of hydrated materials, including almost all biological specimens have to be prepared in various ways to stabilize them, reduce their thickness (ultrathin sectioning) and increase their electron optical contrast (staining). These processes may result in *artifacts*, but these can usually be identified by comparing the results obtained by using radically different specimen preparation methods. It is generally believed by scientists working in the field that as results from various preparation techniques have been compared and that there is no reason that they should all produce similar artifacts, it is reasonable to believe that electron microscopy features correspond with those of living cells. In addition,



False-color SEM image of the filter setae of an Antarctic krill. (Raw electron microscope images carry no color information.)

Pictured: First degree filter setae with V-shaped second degree setae pointing towards the inside of the feeding basket. The purple ball is 1 μm in diameter.

higher-resolution work has been directly compared to results from X-ray crystallography, providing independent confirmation of the validity of this technique. Since the 1980s, analysis of cryofixed, vitrified specimens has also become increasingly used by scientists, further confirming the validity of this technique.^{[12] [13] [14]}

Applications

Semiconductor and data storage

- Circuit edit
- Defect analysis
- Failure analysis

Biology and life sciences

- Diagnostic electron microscopy
- Cryobiology
- Protein localization
- Electron tomography
- Cellular tomography
- Cryo-electron microscopy
- Toxicology
- Biological production and viral load monitoring
- Particle analysis
- Pharmaceutical QC
- Structural biology
- 3D tissue imaging
- Virology
- Vitrification

Research

- Electron beam-induced deposition
- Materials qualification
- Materials and sample preparation
- Nanoprototyping
- Nanometrology
- Device testing and characterization

Industry

- High-resolution imaging
- 2D & 3D micro-characterization
- Macro sample to nanometer metrology
- Particle detection and characterization
- Direct beam-writing fabrication
- Dynamic materials experiments
- Sample preparation
- Forensics
- Mining (mineral liberation analysis)
- Chemical/Petrochemical

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External links

- Science Aid: Electron Microscopy (<http://scienceaid.co.uk/biology/cell/analysingcells.html>) High School (GCSE, A Level) resource
- Cell Centered Database - Electron microscopy data (<http://ccdb.ucsd.edu/sand/main?typeid=4&event=showMPByType&start=1>)

General

- Nanohedron.com Nano image gallery (<http://www.nanohedron.com/>) beautiful images generated with electron microscopes.
- electron microscopy (<http://www.microscopy.ethz.ch>) Website of the ETH Zurich: Very good graphics and images, which illustrate various procedures.
- Environmental Scanning Electron Microscope (ESEM) (<http://www.danilatos.com>)
- X-ray element analysis in electron microscope (http://www.microanalyst.net/index_e.phtml) – Information portal with X-ray microanalysis and EDX contents

History

- John H.L. Watson: Very early Electron Microscopy in the Department of Physics, the University of Toronto – A personal recollection (<http://www.physics.utoronto.ca/overview/history/microsco>)
- Rubin Borasky Electron Microscopy Collection, 1930-1988 (<http://americanhistory.si.edu/archives/d8452.htm>) Archives Center, National Museum of American History, Smithsonian Institution.

Other

- The Royal Microscopical Society, Electron Microscopy Section (UK) (<http://www.rms.org.uk/em.shtml>)
 - Albert Lleal micrograph. Scanning Electron Micrograph Coloured SEM (<http://www.albertlleal.com/microphotography.html>)
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X-ray microscope

An **X-ray microscope** uses electromagnetic radiation in the soft X-ray band to produce images of very small objects. Unlike visible light, X-rays do not reflect or refract easily, and they are invisible to the human eye. Therefore the basic process of an X-ray microscope is to expose film or use a charge-coupled device (CCD) detector to detect X-rays that pass through the specimen. It is a contrast imaging technology using the difference in absorption of soft x-ray in the water window region (wavelength region: 2.3 - 4.4 nm, photon energy region: 0.28 - 0.53 keV) by the carbon atom (main element composing the living cell) and the oxygen atom (main element for water).

Early X-ray microscopes by Paul Kirkpatrick and Albert Baez used grazing-incidence reflective optics to focus the X-rays, which grazed X-rays off parabolic curved mirrors at a very high angle of incidence. An alternative method of focusing X-rays is to use a tiny fresnel zone plate of concentric gold or nickel rings on a silicon dioxide substrate. Sir Lawrence Bragg produced some of the first usable X-ray images with his apparatus in the late 1940's.

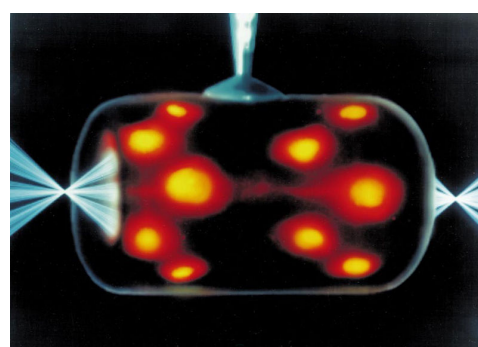
In the 1950's Newberry produced a shadow X-ray microscope which placed the specimen between the source and a target plate, this became the basis for the first commercial X-ray microscopes from the General Electric Company.

The Advanced Light Source (ALS)[1] in Berkeley CA is home to XM-1 (<http://www.cxro.lbl.gov/BL612/>), a full field soft X-ray microscope operated by the Center for X-ray Optics [2] and dedicated to various applications in modern nanoscience, such as nanomagnetic materials, environmental and materials sciences and biology. XM-1 uses an X-ray lens to focus X-rays on a CCD, in a manner similar to an optical microscope. XM-1 still holds the world record in spatial resolution with Fresnel zone plates down to 15nm and is able to combine high spatial resolution with a sub-100ps time resolution to study e.g. ultrafast spin dynamics.

The ALS is also home to the world's first soft x-ray microscope designed for biological and biomedical research. This new instrument, XM-2 was designed and built by scientists from the National Center for X-ray Tomography (<http://ncxt.lbl.gov>). XM-2 is capable of producing 3-Dimensional tomograms of cells.

Sources of soft X-rays suitable for microscopy, such as synchrotron radiation sources, have fairly low brightness of the required wavelengths, so an alternative method of image formation is scanning transmission soft X-ray microscopy. Here the X-rays are focused to a point and the sample is mechanically scanned through the produced focal spot. At each point the transmitted X-rays are recorded with a detector such as a proportional counter or an avalanche photodiode. This type of Scanning Transmission X-ray Microscope (STXM) was first developed by researchers at Stony Brook University and was employed at the National Synchrotron Light Source at Brookhaven National Laboratory.

The resolution of X-ray microscopy lies between that of the optical microscope and the electron microscope. It has an advantage over conventional electron microscopy in that it can view biological samples in their natural state. Electron microscopy is widely used to obtain images with nanometer level resolution but the relatively thick living cell cannot be observed as the sample has to be chemically fixed, dehydrated, embedded in resin, then sliced ultra thin. However, it should be mentioned that cryo-electron microscopy allows the observation of biological specimens in their hydrated natural state, albeit embedded in water ice. Until now, resolutions of 30 nanometer are possible using the Fresnel zone plate lens which forms the image using the soft x-rays emitted from a synchrotron. Recently, the use of soft x-rays emitted from laser-produced plasmas rather than synchrotron radiation is becoming more



Indirect drive laser inertial confinement fusion uses a "hohlraum" which is irradiated with laser beam cones from either side on its inner surface to bathe a fusion microcapsule inside with smooth high intensity X-rays.

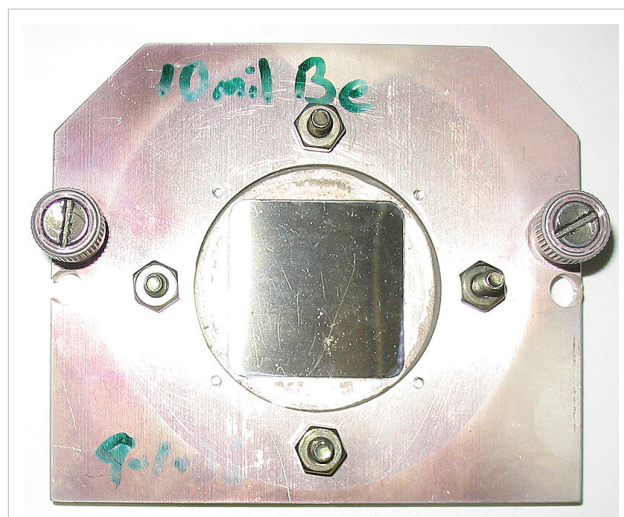
The highest energy X-rays which penetrate the hohlraum can be visualized using an X-ray microscope such as here, where X-radiation is represented in orange/red.

popular.

Additionally, X-rays cause fluorescence in most materials, and these emissions can be analyzed to determine the chemical elements of an imaged object. Another use is to generate diffraction patterns, a process used in X-ray crystallography. By analyzing the internal reflections of a diffraction pattern (usually with a computer program), the three-dimensional structure of a crystal can be determined down to the placement of individual atoms within its molecules. X-ray microscopes are sometimes used for these analyses because the samples are too small to be analyzed in any other way.

External links

- Application of X-ray microscopy in analysis of living hydrated cells ^[3]
- Hard X-ray microbeam experiments with a sputtered-sliced Fresnel zone plate and its applications ^[4]
- Scientific applications of soft x-ray microscopy ^[5]



A square beryllium foil mounted in a steel case to be used as a window between a vacuum chamber and an X-ray microscope. Beryllium, due to its low Z number is highly transparent to X-rays.

References

- [1] <http://www-als.lbl.gov>
- [2] <http://www.cxro.lbl.gov>
- [3] http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12379938
- [4] http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=11972376
- [5] <http://www.cxro.lbl.gov/BL612/index.php?content=research.html>

X-ray computed tomography

X-ray computed tomography (CT) is a medical imaging method employing tomography created by computer processing.^[1] Digital geometry processing is used to generate a three-dimensional image of the inside of an object from a large series of two-dimensional X-ray images taken around a single axis of rotation.^[2]

CT produces a volume of data which can be manipulated, through a process known as "windowing", in order to demonstrate various bodily structures based on their ability to block the X-ray beam. Although historically the images generated were in the

axial or transverse plane, orthogonal to the long axis of the body, modern scanners allow this volume of data to be reformatted in various planes or even as volumetric (3D) representations of structures. Although most common in medicine, CT is also used in other fields, such as nondestructive materials testing. Another example is archaeological uses such as imaging the contents of sarcophagi or the DigiMorph project at the University of Texas at Austin which uses a CT scanner to study biological and paleontological specimens.

Usage of CT has increased dramatically over the last two decades in many countries.^[3] An estimated 72 million scans were performed in the United States in 2007.^[4] It is estimated that 0.4% of current cancers in the United States are due to CTs performed in the past and that this may increase to as high as 1.5-2% with 2007 rates of CT usage.^[5]

Terminology

The word "tomography" is derived from the Greek *tomos* (slice) and *graphein* (to write). Computed tomography was originally known as the "EMI scan" as it was developed at a research branch of EMI, a company best known today for its music and recording business. It was later known as **computed axial tomography** (CAT or CT scan) and **body section röntgenography**.

Although the term "computed tomography" could be used to describe positron emission tomography and single photon emission computed tomography, in practice it usually refers to the computation of tomography from X-ray images, especially in older medical literature and smaller medical facilities.

In MeSH, "computed axial tomography" was used from 1977–79, but the current indexing explicitly includes "X-ray" in the title.^[6]

Diagnostic use

Since its introduction in the 1970s, CT has become an important tool in medical imaging to supplement X-rays and medical ultrasonography. It has more recently been used for preventive medicine or screening for disease, for example CT colonography for patients with a high risk of colon cancer, or full-motion heart scans for patients with high risk of heart disease. A number of institutions offer full-body scans for the general population. This is however a controversial practice, given its cost, significant radiation exposure, lack of proven benefit, and the risk of finding 'incidental' abnormalities that may trigger additional investigations.



A patient is receiving a CT scan for cancer. Outside of the scanning room is an imaging computer that reveals a 3D image of the body's interior.

Head

CT scanning of the head is typically used to detect infarction, tumours, calcifications, haemorrhage and bone trauma. Of the above, hypodense (dark) structures indicate infarction or tumours, hyperdense (bright) structures indicate calcifications and haemorrhage and bone trauma can be seen as disjunction in bone windows.

Chest

CT can be used for detecting both acute and chronic changes in the lung parenchyma, that is, the internals of the lungs. It is particularly relevant here because normal two-dimensional x-rays do not show such defects. A variety of different techniques are used, depending on the suspected abnormality. For evaluation of chronic interstitial processes (emphysema, fibrosis, and so forth), thin sections with high spatial frequency reconstructions are used; often scans are performed both in inspiration and expiration. This special technique is called High Resolution CT (HRCT). HRCT is normally done with thin sections with skipped areas between the thin sections. Therefore it produces a sampling of the lung and not continuous images. Continuous images are provided in a standard CT of the chest.

For detection of airspace disease (such as pneumonia) or cancer, relatively thick sections and genera-purpose image reconstruction techniques may be adequate. IV contrast may also be used as it clarifies the anatomy and boundaries of the great vessels and improves assessment of the mediastinum and hilar regions for lymphadenopathy; this is particularly important for accurate assessment of cancer.

CT angiography of the chest is also becoming the primary method for detecting pulmonary embolism (PE) and aortic dissection, and requires accurately timed rapid injections of contrast (Bolus Tracking) and high-speed helical scanners. CT is the standard method of evaluating abnormalities seen on chest X-ray and of following findings of uncertain acute significance. Cardiac CTA is now being used to diagnose coronary artery disease.

According to the 2007 *New England Journal of Medicine* study, 19.2 million (31%) of the 62 million CTs done every year are for lung CTs.

Pulmonary angiogram

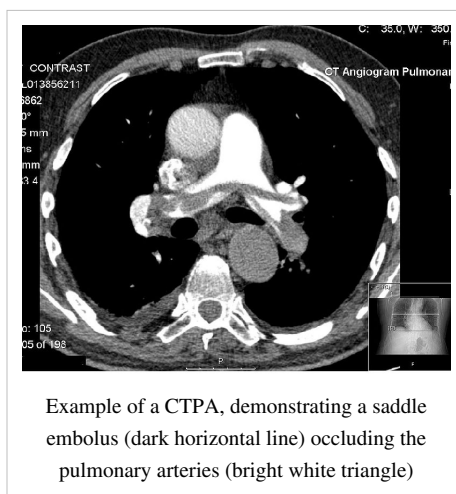
CT pulmonary angiogram (CTPA) is a medical diagnostic test used to diagnose pulmonary embolism (PE). It employs computed tomography to obtain an image of the pulmonary arteries.

It is a preferred choice of imaging in the diagnosis of PE due to its minimally invasive nature for the patient, whose only requirement for the scan is a cannula (usually a 20G).

MDCT (multi detector CT) scanners give the optimum resolution and image quality for this test. Images are usually taken on a 0.625 mm slice thickness, although 2 mm is sufficient. 50–100 mls of contrast is given to the patient at a rate of 4 ml/s. The tracker/locator is placed at the level of the pulmonary arteries, which sit roughly at the level of the carina. Images are acquired with the maximum intensity of radio-opaque contrast in the pulmonary arteries. This is done using bolus tracking.

CT machines are now so sophisticated that the test can be done with a patient visit of 5 minutes with an approximate scan time of only 5 seconds or less.

A normal CTPA scan will show the contrast filling the pulmonary vessels, appearing as bright white. Ideally the aorta should be empty of contrast, to reduce any partial volume artifact which may result in a false positive. Any



mass filling defects, such as an embolus, will appear dark in place of the contrast, filling / blocking the space where blood should be flowing into the lungs.

Cardiac

With the advent of subsecond rotation combined with multi-slice CT (up to 320-slices), high resolution and high speed can be obtained at the same time, allowing excellent imaging of the coronary arteries (cardiac CT angiography). Images with an even higher temporal resolution can be formed using retrospective ECG gating. In this technique, each portion of the heart is imaged more than once while an ECG trace is recorded. The ECG is then used to correlate the CT data with their corresponding phases of cardiac contraction. Once this correlation is complete, all data that were recorded while the heart was in motion (systole) can be ignored and images can be made from the remaining data that happened to be acquired while the heart was at rest (diastole). In this way, individual frames in a cardiac CT investigation have a better temporal resolution than the shortest tube rotation time.

Because the heart is effectively imaged more than once (as described above), cardiac CT angiography results in a relatively high radiation exposure around 12 mSv. Currently, newer acquisition protocols have been developed drastically reducing the xRays radiation exposure, down to 1 milliSievert (cfr. Pavone, Fioranelli, Dowe: *Computed Tomography or Coronary Arteries*, Springer 2009). For the sake of comparison, a chest X-ray carries a dose of approximately 0.02^[7] to 0.2 mSv and natural background radiation exposure is around 0.01 mSv/day. Thus, cardiac CTA is equivalent to approximately 100-600 chest X-rays or over 3 years worth of natural background radiation. Methods are available to decrease this exposure, however, such as prospectively decreasing radiation output based on the concurrently acquired ECG (aka tube current modulation.) This can result in a significant decrease in radiation exposure, at the risk of compromising image quality if there is any arrhythmia during the acquisition. The significance of radiation doses in the diagnostic imaging range has not been proven, although the possibility of inducing an increased cancer risk across a population is a source of significant concern. This potential risk must be weighed against the competing risk of not performing a test and potentially not diagnosing a significant health problem such as coronary artery disease.

It is uncertain whether this modality will replace invasive coronary catheterization. Currently, it appears that the greatest utility of cardiac CT lies in ruling out coronary artery disease rather than ruling it in. This is because the test has a high sensitivity (greater than 90%) and thus a negative test result means that a patient is very unlikely to have coronary artery disease and can be worked up for other causes of their chest symptoms. This is termed a high negative predictive value. A positive result is less conclusive and often will be confirmed (and possibly treated) with subsequent invasive angiography. The positive predictive value of cardiac CTA is estimated at approximately 82% and the negative predictive value is around 93%.

Dual Source CT scanners, introduced in 2005, allow higher temporal resolution by acquiring a full CT slice in only half a rotation, thus reducing motion blurring at high heart rates and potentially allowing for shorter breath-hold time. This is particularly useful for ill patients who have difficulty holding their breath or who are unable to take heart-rate lowering medication.

The speed advantages of 64-slice MSCT have rapidly established it as the minimum standard for newly installed CT scanners intended for cardiac scanning. Manufacturers have developed 320-slice and true 'volumetric' scanners, primarily for their improved cardiac scanning performance.

The latest MSCT scanners acquire images only at 70-80% of the R-R interval (late diastole). This prospective gating can reduce effective dose from 10-15mSv to as little as 1.2mSv in follow-up patients acquiring at 75% of the R-R interval. Effective doses at a centre with well trained staff doing coronary imaging can average less than the doses for conventional coronary angiography.

Abdominal and pelvic

CT is a sensitive method for diagnosis of abdominal diseases. It is used frequently to determine stage of cancer and to follow progress. It is also a useful test to investigate acute abdominal pain (especially of the lower quadrants, whereas ultrasound is the preferred first line investigation for right upper quadrant pain). Renal stones, appendicitis, pancreatitis, diverticulitis, abdominal aortic aneurysm, and bowel obstruction are conditions that are readily diagnosed and assessed with CT. CT is also the first line for detecting solid organ injury after trauma.

Multidetector CT (MDCT) can clearly delineate anatomic structures in the abdomen, which is critical in the diagnosis of internal diaphragmatic and other nonpalpable or unsuspected hernias. MDCT also offers clear detail of the abdominal wall allowing wall hernias to be identified accurately.^[8]

Oral and/or rectal contrast may be used depending on the indications for the scan. A dilute (2% w/v) suspension of barium sulfate is most commonly used. The concentrated barium sulfate preparations used for fluoroscopy e.g. barium enema are too dense and cause severe artifacts on CT. Iodinated contrast agents may be used if barium is contraindicated (for example, suspicion of bowel injury). Other agents may be required to optimize the imaging of specific organs, such as rectally administered gas (air or carbon dioxide) or fluid (water) for a colon study, or oral water for a stomach study.

CT has limited application in the evaluation of the *pelvis*. For the female pelvis in particular, ultrasound and MRI are the imaging modalities of choice. Nevertheless, it may be part of abdominal scanning (e.g. for tumors), and has uses in assessing fractures.

CT is also used in osteoporosis studies and research alongside dual energy X-ray absorptiometry (DXA). Both CT and DXA can be used to assess bone mineral density (BMD) which is used to indicate bone strength, however CT results do not correlate exactly with DXA (the gold standard of BMD measurement). CT is far more expensive, and subjects patients to much higher levels of ionizing radiation, so it is used infrequently.

Extremities

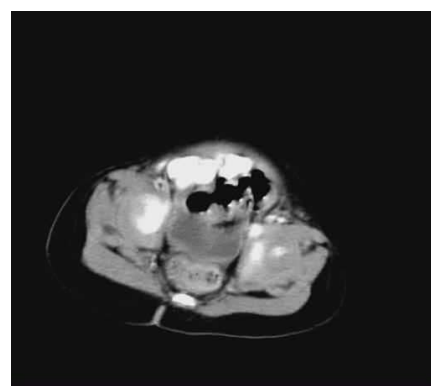
CT is often used to image complex fractures, especially ones around joints, because of its ability to reconstruct the area of interest in multiple planes. Fractures, ligamentous injuries and dislocations can easily be recognised with a 0.2 mm resolution.^{[9] [10]}

Advantages and disadvantages

Advantages over traditional radiography

There are several advantages that CT has over traditional 2D medical radiography. First, CT completely eliminates the superimposition of images of structures outside the area of interest. Second, because of the inherent high-contrast resolution of CT, differences between tissues that differ in physical density by less than 1% can be distinguished. Finally, data from a single CT imaging procedure consisting of either multiple contiguous or one helical scan can be viewed as images in the axial, coronal, or sagittal planes, depending on the diagnostic task. This is referred to as multiplanar reformatted imaging.

CT is regarded as a moderate to high radiation diagnostic technique. While technical advances have improved radiation efficiency, there has been simultaneous pressure to obtain higher-resolution imaging and use more complex



CT Scan of 11 cm **Wilms' tumor** of right kidney in 13 month old patient.

scan techniques, both of which require higher doses of radiation. The improved resolution of CT has permitted the development of new investigations, which may have advantages; compared to conventional angiography for example, CT angiography avoids the invasive insertion of an arterial catheter and guidewire; CT colonography (also known as virtual colonoscopy or VC for short) may be as useful as a barium enema for detection of tumors, but may use a lower radiation dose. CT VC is increasingly being used in the UK as a diagnostic test for bowel cancer and can negate the need for a colonoscopy.

The greatly increased availability of CT, together with its value for an increasing number of conditions, has been responsible for a large rise in popularity. So large has been this rise that, in the most recent comprehensive survey in the United Kingdom, CT scans constituted 7% of all radiologic examinations, but contributed 47% of the total collective dose from medical X-ray examinations in 2000/2001.^[11] Increased CT usage has led to an overall rise in the total amount of medical radiation used, despite reductions in other areas. In the United States and Japan for example, there were 26 and 64 CT scanners per 1 million population in 1996. In the U.S., there were about 3 million CT scans performed in 1980, compared to an estimated 62 million scans in 2006.^[12]

The radiation dose for a particular study depends on multiple factors: volume scanned, patient build, number and type of scan sequences, and desired resolution and image quality. Additionally, two helical CT scanning parameters that can be adjusted easily and that have a profound effect on radiation dose are tube current and pitch.^[13]

Computed tomography (CT) scan has been shown to be more accurate than radiographs in evaluating anterior interbody fusion but may still over-read the extent of fusion.^[14]

Safety concerns

The increased use of CT scans has been the greatest in two fields: screening of adults (screening CT of the lung in smokers, virtual colonoscopy, CT cardiac screening and whole-body CT in asymptomatic patients) and CT imaging of children. Shortening of the scanning time to around 1 second, eliminating the strict need for subject to remain still or be sedated, is one of the main reasons for large increase in the pediatric population (especially for the diagnosis of appendicitis).^[12] CT scans of children have been estimated to produce non-negligible increases in the probability of lifetime cancer mortality, leading to calls for the use of reduced current settings for CT scans of children.^[15] These calculations are based on the assumption of a linear relationship between radiation dose and cancer risk; this claim is controversial, as some but not all evidence shows that smaller radiation doses are not harmful.^[12] Estimated lifetime cancer mortality risks attributable to the radiation exposure from a CT in a 1-year-old are 0.18% (abdominal) and 0.07% (head)—an order of magnitude higher than for adults—although those figures still represent a small increase in cancer mortality over the background rate. In the United States, of approximately 600,000 abdominal and head CT examinations annually performed in children under the age of 15 years, a rough estimate is that 500 of these individuals might ultimately die from cancer attributable to the CT radiation.^[16] The additional risk is still very low (0.35%) compared to the background risk of dying from cancer (23%).^[16] However, if these statistics are extrapolated to the current number of CT scans, the additional rise in cancer mortality could be 1.5 to 2%. Furthermore, certain conditions can require children to be exposed to multiple CT scans. Again, these calculations can be problematic because the assumptions underlying them could overestimate the risk.^[12]

In 2009 a number of studies appeared that further defined the risk of cancer that may be caused by CT scans.^[17] One study indicated that radiation by CT scans is often higher and more variable than cited and each of the 19,500 CT scans that are daily performed in the US is equivalent to 30 to 442 chest x-rays in radiation. It has been estimated that CT radiation exposure will result in 29,000 new cancer cases just from the CT scans performed in 2007.^[17] The most common cancers caused by CT are thought to be lung cancer, colon cancer and leukemia with younger people and women more at risk. These conclusions, however, are criticized by the American College of Radiology (ACR) that maintains that the life expectancy of CT scanned patients is not that of the general population and that the model of calculating cancer is based on total body radiation exposure and thus faulty.^[17]

CT scans can be performed with different settings for lower exposure in children, although these techniques are often not employed. Surveys have suggested that currently, many CT scans are performed unnecessarily. Ultrasound scanning or magnetic resonance imaging are alternatives (for example, in appendicitis or brain imaging) without the risk of radiation exposure. Although CT scans come with an additional risk of cancer (it can be estimated that the radiation exposure from a full body scan is the same as standing 2.4 km away from the WWII atomic bomb blasts in Japan^{[18] [19]}), especially in children, the benefits that stem from their use outweighs the risk in many cases.^[16] Studies support informing parents of the risks of pediatric CT scanning.^[20]

Typical scan doses

Examination	Typical effective dose (mSv)	(millirem)
X-ray Personnel security screening scan	0.00025	0.025 ^[21]
Chest X-ray	0.1	10
Head CT	1.5 ^[22]	150
Screening mammography	3 ^[12]	300
Abdomen CT	5.3 ^[22]	530
Chest CT	5.8 ^[22]	580
CT colonography (virtual colonoscopy)	3.6–8.8	360–880
Chest, abdomen and pelvis CT	9.9 ^[22]	990
Cardiac CT angiogram	6.7–13 ^[23]	670–1300
Barium enema	15 ^[12]	1500
Neonatal abdominal CT	20 ^[12]	2000

For purposes of comparison, the average background exposure in the UK is 1-3 mSv per year.

Adverse reactions to contrast agents

Because contrast CT scans rely on intravenously administered contrast agents in order to provide superior image quality, there is a low but non-negligible level of risk associated with the contrast agents themselves. Many patients report nausea and discomfort, including warmth in the crotch which mimics the sensation of wetting oneself. Certain patients may experience severe and potentially life-threatening allergic reactions to the contrast dye.

The contrast agent may also induce kidney damage. The risk of this is increased with patients who have preexisting renal insufficiency, preexisting diabetes, or reduced intravascular volume. In general, if a patient has normal kidney function, then the risks of contrast nephropathy are negligible. Patients with mild kidney impairment are usually advised to ensure full hydration for several hours before and after the injection. For moderate kidney failure, the use of iodinated contrast should be avoided; this may mean using an alternative technique instead of CT, e.g., MRI. Paradoxically, patients with severe renal failure requiring dialysis do not require special precautions, as their kidneys have so little function remaining that any further damage would not be noticeable and the dialysis will remove the contrast agent.

Low-dose CT scan

An important issue within radiology today is how to reduce the radiation dose during CT examinations without compromising the image quality. Generally, higher radiation doses result in higher-resolution images, while lower doses lead to increased image noise and unsharp images. Increased dosage raises the risk of radiation induced cancer — a four-phase abdominal CT gives the same radiation dose as 300 chest x-rays. Several methods exist which can reduce the exposure to ionizing radiation during a CT scan.

1. New software technology can significantly reduce the required radiation dose. The software works as a filter that reduces random noise and enhances structures. In this way, it is possible to get high-quality images and at the same time lower the dose by as much as 30 to 70 percent.
2. Individualize the examination and adjust the radiation dose to the body type and body organ examined. Different body types and organs require different amounts of radiation.
3. Prior to every CT examination, evaluate the appropriateness of the exam whether it is motivated or if another type of examination is more suitable. Higher resolution is not always suitable for any given scenario, such as detection of small pulmonary masses^[24]

Computed tomography versus MRI

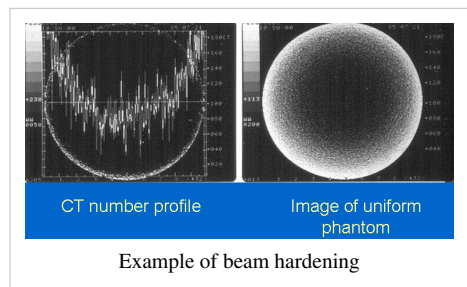
The basic mathematics of the 2D-Fourier transform in CT reconstruction is very similar to the 2D-FT NMRI, but the computer data processing in CT does differ in detail, as for example in the case of the volume rendering and artifact elimination algorithms that are specific to CT.

Artifacts

Although CT is a relatively accurate test, it is liable to produce artifacts, such as the following:^[2], Chapters 3 and 5

- Aliasing artifact or streaks

These appear as dark lines which radiate away from sharp corners. It occurs because it is impossible for the scanner to "sample" or take enough projections of the object, which is usually metallic. It can also occur when an insufficient X-ray tube current is selected, and insufficient penetration of the x-ray occurs. These artifacts are also closely tied to motion during a scan. This type of artifact commonly occurs in head images around the pituitary fossa area.



- Partial volume effect

This appears as "blurring" over sharp edges. It is due to the scanner being unable to differentiate between a small amount of high-density material (e.g. bone) and a larger amount of lower density (e.g., cartilage). The processor tries to average out the two densities or structures, and information is lost. This can be partially overcome by scanning using thinner slices.

- Ring artifact

Probably the most common mechanical artifact, the image of one or many "rings" appears within an image. This is usually due to a detector fault.

- Noise artifact

This appears as graining on the image and is caused by a low signal to noise ratio. This occurs more commonly when a thin slice thickness is used. It can also occur when the power supplied to the X-ray tube is insufficient to penetrate the anatomy.

- Motion artifact

This is seen as blurring and/or streaking which is caused by movement of the object being imaged.

- Windmill

Streaking appearances can occur when the detectors intersect the reconstruction plane. This can be reduced with filters or a reduction in pitch.

- Beam hardening

This can give a "cupped appearance". It occurs when there is more attenuation in the center of the object than around the edge. This is easily corrected by filtration and software.

Prevalence

Usage of CT has increased dramatically over the last two decades.^[3] An estimated 72 million scans were performed in the United States in 2007.^[4] In Calgary Canada 12.1% of people who present to the emergency with an urgent complaint received a CT scan, most commonly either of the head or the abdomen. The percentage who received CT however varied markedly by the emergency physician who saw them from 1.8% to 25%.^[25] In the emergency department in the United States CT or MRI imaging is done in 15% of people who present with injuries as of 2007 (up from 6% in 1998).^[26]

Process

X-ray slice data is generated using an X-ray source that rotates around the object; X-ray sensors are positioned on the opposite side of the circle from the X-ray source. The earliest sensors were scintillation detectors, with photomultiplier tubes excited by (typically) cesium iodide crystals. Cesium iodide was replaced during the 1980s by ion chambers containing high pressure Xenon gas. These systems were in turn replaced by scintillation systems based on photo diodes instead of photomultipliers and modern scintillation materials with more desirable characteristics. Many data scans are progressively taken as the object is gradually passed through the gantry.

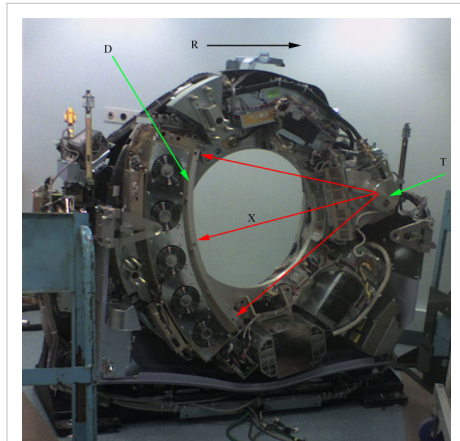
Newer machines with faster computer systems and newer software strategies can process not only individual cross sections but continuously changing cross sections as the gantry, with the object to be imaged, is slowly and smoothly slid through the X-ray circle. These are called *helical* or *spiral CT* machines. Their computer systems integrate the data of the moving individual slices to generate three dimensional volumetric information (3D-CT scan), in turn viewable from multiple different perspectives on attached CT workstation monitors. This type of data acquisition requires enormous processing power, as the data are arriving in a continuous stream and must be processed in real-time.

In conventional CT machines, an X-ray tube and detector are physically rotated behind a circular shroud (see the image above right); in the electron beam tomography (EBT) the tube is far larger and higher power to support the high temporal resolution. The electron beam is deflected in a hollow funnel-shaped vacuum chamber. X-rays are generated when the beam hits the stationary target. The detector is also stationary. This arrangement can result in very fast scans, but is extremely expensive.

CT is used in medicine as a diagnostic tool and as a guide for interventional procedures. Sometimes contrast materials such as intravenous iodinated contrast are used. This is useful to highlight structures such as blood vessels that otherwise would be difficult to delineate from their surroundings. Using contrast material can also help to obtain functional information about tissues.

Once the scan data has been acquired, the data must be processed using a form of tomographic reconstruction, which produces a series of cross-sectional images. The most common technique in general use is filtered back projection, which is straight-forward to implement and can be computed rapidly. Mathematically, this method is based on the Radon transform. However, this is not the only technique available: the original EMI scanner solved the tomographic reconstruction problem by linear algebra, but this approach was limited by its high computational complexity, especially given the computer technology available at the time. More recently, manufacturers have developed iterative physical model-based expectation-maximization techniques. These techniques are advantageous because they use an internal model of the scanner's physical properties and of the physical laws of X-ray interactions. By contrast, earlier methods have assumed a perfect scanner and highly simplified physics, which leads to a number of artefacts and reduced resolution - the result is images with improved resolution, reduced noise and fewer artefacts, as well as the ability to greatly reduce the radiation dose in certain circumstances. The disadvantage is a very high computational requirement, which is at the limits of practicality for current scan protocols.

Pixels in an image obtained by CT scanning are displayed in terms of relative radiodensity. The pixel itself is displayed according to the mean attenuation of the tissue(s) that it corresponds to on a scale from +3071 (most attenuating) to -1024 (least attenuating) on the Hounsfield scale. Pixel is a two dimensional unit based on the matrix size and the field of view. When the CT slice thickness is also factored in, the unit is known as a Voxel, which is a three dimensional unit. The phenomenon that one part of the detector cannot differentiate between different tissues is called the "*Partial Volume Effect*". That means that a big amount of cartilage and a thin layer of compact bone can cause the same attenuation in a voxel as hyperdense cartilage alone. Water has an attenuation of 0 Hounsfield units (HU) while air is -1000 HU, cancellous bone is typically +400 HU, cranial bone can reach 2000 HU or more (os temporale) and can cause artifacts. The attenuation of metallic implants depends on atomic number of the element used: Titanium usually has an amount of +1000 HU, iron steel can completely extinguish the X-ray and is therefore responsible for well-known line-artifacts in computed tomograms. Artifacts are caused by abrupt transitions between low- and high-density materials, which results in data values that exceed the dynamic range of the processing electronics.



CT scanner with cover removed to show the principle of operation

Three-dimensional reconstruction

The principle

Because contemporary CT scanners offer isotropic or near isotropic, resolution, display of images does not need to be restricted to the conventional axial images. Instead, it is possible for a software program to build a volume by "stacking" the individual slices one on top of the other. The program may then display the volume in an alternative manner.^[27]

Multiplanar reconstruction

Multiplanar reconstruction (MPR) is the simplest method of reconstruction. A volume is built by stacking the axial slices. The software then cuts slices through the volume in a different plane (usually orthogonal). Optionally, a special projection method, such as maximum-intensity projection (MIP) or minimum-intensity projection (mIP), can be used to build the reconstructed slices.

MPR is frequently used for examining the spine. Axial images through the spine will only show one vertebral body at a time and cannot reliably show the intervertebral discs. By reformatting the volume, it becomes much easier to visualise the position of one vertebral body in relation to the others.

Modern software allows reconstruction in non-orthogonal (oblique) planes so that the optimal plane can be chosen to display an anatomical structure. This may be particularly useful for visualising the structure of the bronchi as these do not lie orthogonal to the direction of the scan.

For vascular imaging, curved-plane reconstruction can be performed. This allows bends in a vessel to be "straightened" so that the entire length can be visualised on one image, or a short series of images. Once a vessel has been "straightened" in this way, quantitative measurements of length and cross sectional area can be made, so that surgery or interventional treatment can be planned.

MIP reconstructions enhance areas of high radiodensity, and so are useful for angiographic studies. mIP reconstructions tend to enhance air spaces so are useful for assessing lung structure.

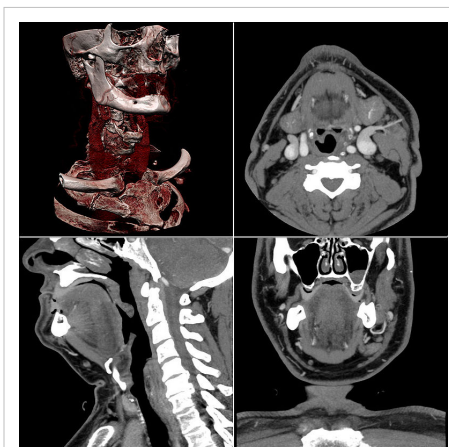
3D rendering techniques

Surface rendering

A threshold value of radiodensity is set by the operator (e.g. a level that corresponds to bone). From this, a three-dimensional model can be constructed using edge detection image processing algorithms and displayed on screen. Multiple models can be constructed from various different thresholds, allowing different colors to represent each anatomical component such as bone, muscle, and cartilage. However, the interior structure of each element is not visible in this mode of operation.

Volume rendering

Surface rendering is limited in that it will only display surfaces which meet a threshold density, and will only display the surface that is closest to the imaginary viewer. In volume rendering, transparency and colors are used to allow a better representation of the volume to be shown in a single image—e.g. the bones of the pelvis could be displayed as semi-transparent, so that even at an oblique angle, one part of the image does not conceal another.



Typical screen layout for diagnostic software, showing one 3D and three MPR views

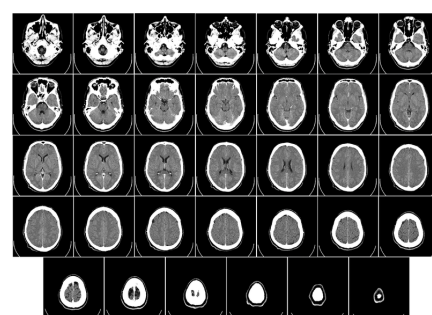
Image segmentation

Where different structures have similar radiodensity, it can become impossible to separate them simply by adjusting volume rendering parameters. The solution is called segmentation, a manual or automatic procedure that can remove the unwanted structures from the image.

Example

Some slices of a cranial CT scan are shown below. The bones are whiter than the surrounding area. (Whiter means higher attenuation.) Note the blood vessels (arrowed) showing brightly due to the injection of an iodine-based contrast agent.

A volume rendering of this volume clearly shows the high density bones.



Computed tomography of human brain, from base of the skull to top. Taken with intravenous contrast medium.

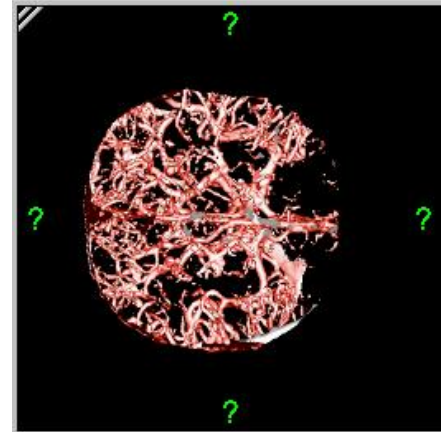
After using a segmentation tool to remove the bone, the previously concealed vessels can now be demonstrated.



Bone reconstructed in 3D

Industrial computed tomography

Industrial CT Scanning (Industrial Computed Tomography) is a process which utilizes x-ray equipment to produce 3D representations of components both externally and internally. Industrial CT scanning has been utilized in many areas of industry for internal inspection of components. Some of the key uses for CT scanning have been flaw detection, failure analysis, metrology, assembly analysis and reverse engineering applications



Brain vessels reconstructed in 3D after bone has been removed by segmentation

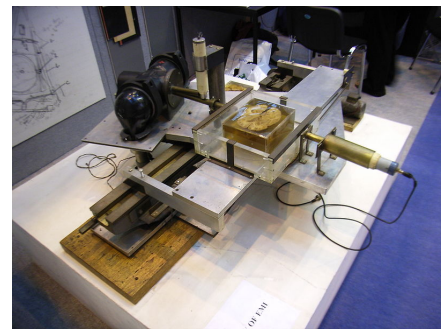
History

In the early 1900s, the Italian radiologist Alessandro Vallebona proposed a method to represent a single slice of the body on the radiographic film. This method was known as tomography. The idea is based on simple principles of projective geometry: moving synchronously and in opposite directions the X-ray tube and the film, which are connected together by a rod whose pivot point is the focus; the image created by the points on the focal plane appears sharper, while the images of the other points annihilate as noise. This is only marginally effective, as blurring occurs in only the "x" plane. There are also more complex devices which can move in more than one plane and perform more effective blurring.

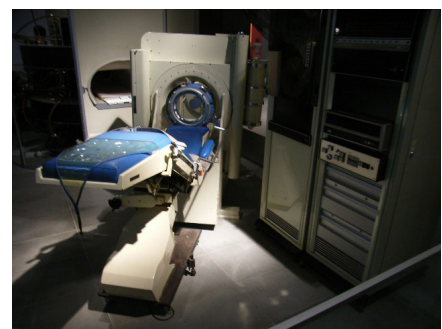
Tomography had been one of the pillars of radiologic diagnostics until the late 1970s, when the availability of minicomputers and of the transverse axial scanning method – this last due to the work of Godfrey Hounsfield and South African-born Allan McLeod Cormack – gradually supplanted it as the modality of CT. Mathematically, the method is based upon the use of the Radon Transform invented by Johann Radon in 1917. But as Cormack remembered later,^[28] he had to find the solution himself since it was only in 1972 that he learned of the work of Radon, by chance.

The first commercially viable CT scanner was invented by Sir Godfrey Hounsfield in Hayes, United Kingdom, at EMI Central Research Laboratories using X-rays. Hounsfield conceived his idea in 1967.^[29] The first EMI-Scanner was installed at Atkinson Morley Hospital in Wimbledon, England, and the first patient brain-scan was done on 1 October 1971.^[30] It was publicly announced in 1972.

The original 1971 prototype took 160 parallel readings through 180 angles, each 1° apart, with each scan taking a little over 5 minutes. The images from these scans took 2.5 hours to be processed by algebraic reconstruction techniques on a large computer. The scanner had a single photomultiplier detector, and operated on the Translate/Rotate principle.^[30]



The prototype CT scanner



A historic EMI-Scanner

It has been claimed that thanks to the success of The Beatles, EMI could fund research and build early models for medical use.^[31] The first production X-ray CT machine (in fact called the "EMI-Scanner") was limited to making tomographic sections of the brain, but acquired the image data in about 4 minutes (scanning two adjacent slices), and the computation time (using a Data General Nova minicomputer) was about 7 minutes per picture. This scanner required the use of a water-filled Perspex tank with a pre-shaped rubber "head-cap" at the front, which enclosed the patient's head. The water-tank was used to reduce the dynamic range of the radiation reaching the detectors (between scanning outside the head compared with scanning through the bone of the skull). The images were relatively low resolution, being composed of a matrix of only 80 x 80 pixels.

In the U.S., the first installation was at the Mayo Clinic. As a tribute to the impact of this system on medical imaging the Mayo Clinic has an EMI scanner on display in the Radiology Department. Allan McLeod Cormack of Tufts University in Massachusetts independently invented a similar process, and both Hounsfield and Cormack shared the 1979 Nobel Prize in Medicine.^{[32] [33]}

The first CT system that could make images of any part of the body and did not require the "water tank" was the ACTA (Automatic Computerized Transverse Axial) scanner designed by Robert S. Ledley, DDS, at Georgetown University. This machine had 30 photomultiplier tubes as detectors and completed a scan in only 9 translate/rotate cycles, much faster than the EMI-scanner. It used a DEC PDP11/34 minicomputer both to operate the servo-mechanisms and to acquire and process the images. The Pfizer drug company acquired the prototype from the university, along with rights to manufacture it. Pfizer then began making copies of the prototype, calling it the "200FS" (FS meaning Fast Scan), which were selling as fast as they could make them. This unit produced images in a 256x256 matrix, with much better definition than the EMI-Scanner's 80x80.

Previous studies

A form of tomography can be performed by moving the X-ray source and detector during an exposure. Anatomy at the target level remains sharp, while structures at different levels are blurred. By varying the extent and path of motion, a variety of effects can be obtained, with variable depth of field and different degrees of blurring of "out of plane" structures.^{[34] :25}

Although largely obsolete, conventional tomography is still used in specific situations such as dental imaging (orthopantomography) or in intravenous urography.

Tomosynthesis

Digital tomosynthesis combines digital image capture and processing with simple tube/detector motion as used in conventional radiographic tomography. Although there are some similarities to CT, it is a separate technique. In CT, the source/detector makes a complete 360-degree rotation about the subject obtaining a complete set of data from which images may be reconstructed. In digital tomosynthesis, only a small rotation angle (e.g. 40 degrees) with a small number of discrete exposures (e.g. 10) are used. This incomplete set of data can be digitally processed to yield images similar to conventional tomography with a limited depth of field. However, because the image processing is digital, a series of slices at different depths and with different thicknesses can be reconstructed from the same acquisition, saving both time and radiation exposure.

Because the data acquired are incomplete, tomosynthesis is unable to offer the extremely narrow slice widths that CT offers. However, higher resolution detectors can be used, allowing very high in-plane resolution, even if the Z-axis resolution is poor. The primary interest in tomosynthesis is in breast imaging, as an extension to mammography, where it may offer better detection rates with little extra increase in radiation exposure.

Reconstruction algorithms for tomosynthesis are significantly different from those of conventional CT because the conventional filtered back projection algorithm requires a complete set of data. Iterative algorithms based upon expectation maximization are most commonly used, but are extremely computationally intensive. Some manufacturers have produced practical systems using off-the-shelf GPUs to perform the reconstruction.

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External links

- Open-source computed tomography simulator with educational tracing displays (<http://ctsim.org>)
- idoimaging.com: Free software for viewing CT and other medical imaging files (<http://www.idoimaging.com>)
- CT Artefacts (<http://www.impactscan.org/slides/impactcourse/artefacts/img0.html>) by David Platten
- DigiMorph (<http://digimorph.org/>) A library of 3D imagery based on CT scans of the internal and external structure of living and extinct plants and animals.
- MicroCT and calcified tissues (http://www.med.univ-angers.fr/discipline/lab_histo/page_microCT.htm) A website dedicated to microCT in the microscopic analysis of calcified tissues.
- Free Radiology Resource for Radiologists, Radiographers, and Technical Assistance (<http://www.mdct.com.au>.)
- Radiation Risk Calculator (<http://www.xrayrisk.com>) Calculate cancer risk from CT scans and xrays.
- CT scanner video - gantry (<http://www.radrounds.com/video/ct-scanner-gantry-full-speed>)
- CT in your clinical practice (<http://www.ajronline.org/cgi/data/183/3/DC1/1>) by Gregory J. Kohs and Joel Legunn.
- Coronary CT angiography by Eugene Lin (<http://emedicine.medscape.com/article/1603072-overview>)
- CT physics lecture (http://www.radiolopolis.com/index.php/radiology-videos/video-gallery.html?task=viewvideo&video_id=122) excellent video lectures about physics in computed tomography
- Video documentary of patient getting a CT Scan (http://www.rosiescancerfund.com/videos/view/rosies-ct-scan_67.html)
- Atlas of Radiological Images (<http://atlas.mudr.org>) on atlas.mudr.org. Hundreds of imaging cases and thousands of radiological images sorted by method, topography, organs, with short description.

Positron emission tomography

Positron emission tomography (PET) is a nuclear medicine imaging technique which produces a three-dimensional image or picture of functional processes in the body. The system detects pairs of gamma rays emitted indirectly by a positron-emitting radionuclide (tracer), which is introduced into the body on a biologically active molecule. Images of tracer concentration in 3-dimensional or 4-dimensional space (the 4th dimension being time) within the body are then reconstructed by computer analysis. In modern scanners, this reconstruction is often accomplished with the aid of a CT X-ray scan performed on the patient during the same session, in the same machine.

If the biologically active molecule chosen for PET is FDG, an analogue of glucose, the concentrations of tracer imaged then give tissue metabolic activity, in terms of regional glucose uptake. Although use of this tracer results in the most common type of PET scan, other tracer molecules are used in PET to image the tissue concentration of many other types of molecules of interest.

History

The concept of emission and transmission tomography was introduced by David E. Kuhl and Roy Edwards in the late 1950s. Their work later led to the design and construction of several tomographic instruments at the University of Pennsylvania. Tomographic imaging techniques were further developed by Michel Ter-Pogossian, Michael E. Phelps and others at the Washington University School of Medicine.^{[1] [2]}

Work by Gordon Brownell, Charles Burnham and their associates at the Massachusetts General Hospital beginning in the 1950s contributed significantly to the development of PET technology and included the first demonstration of annihilation radiation for medical imaging.^[3] Their innovations, including the use of light pipes, and volumetric analysis have been important in the deployment of PET imaging. In 1961, James Robertson and his associates at Brookhaven National Laboratory built the first single-plane PET scan, nicknamed the "head-shrinker."^[4]

It is interesting that one of the factors most responsible for the acceptance of positron imaging was the development of radiopharmaceuticals. In particular, the development of labeled 2-fluorodeoxy-D-glucose (2FDG) by the Brookhaven group under the direction of Al Wolf and Joanna Fowler was a major factor in expanding the scope of PET imaging.^[5] The compound was first administered to two normal human volunteers by Abass Alavi in August 1976 at the University of Pennsylvania. Brain images obtained with an ordinary (non-PET) nuclear scanner demonstrated the concentration of FDG in that organ. Later, the substance was used in dedicated positron tomographic scanners, to yield the modern procedure.



Image of a typical positron emission tomography (PET) facility



PET/CT-System with 16-slice CT; the ceiling mounted device is an injection pump for CT contrast agent

The logical extension of positron instrumentation was a design using two 2-dimensional arrays. PC-I was the first instrument using this concept and was designed in 1968, completed in 1969 and reported in 1972. The first applications of PC-I in tomographic mode as distinguished from the computed tomographic mode were reported in 1970.^[6] It soon became clear to many of those involved in PET development that a circular or cylindrical array of detectors was the logical next step in PET instrumentation. Although many investigators took this approach, James Robertson^[7] and Z.H. Cho^[8] were the first to propose a ring system which has become the prototype of the current shape of PET.

The PET/CT scanner, attributed to Dr David Townsend and Dr Nutt was named by TIME Magazine as the medical invention of the year in 2000.

Description

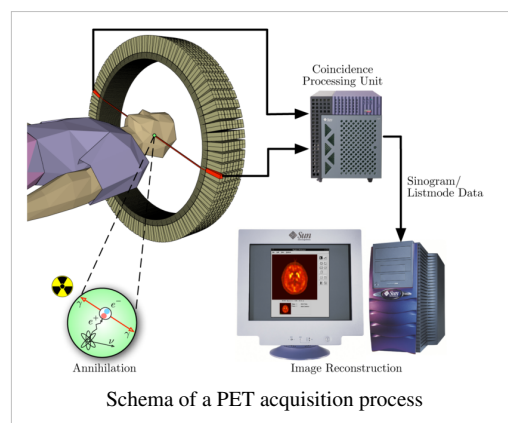
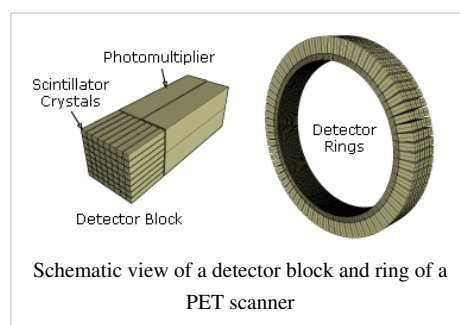
Operation

To conduct the scan, a short-lived radioactive tracer isotope is injected into the living subject (usually into blood circulation). The tracer is chemically incorporated into a biologically active molecule. There is a waiting period while the active molecule becomes concentrated in tissues of interest; then the subject is placed in the imaging scanner. The molecule most commonly used for this purpose is fluorodeoxyglucose (FDG), a sugar, for which the waiting period is typically an hour. During the scan a record of tissue concentration is made as the tracer decays.

As the radioisotope undergoes positron emission decay (also known as positive beta decay), it emits a positron, an antiparticle of the electron with opposite charge. The emitted positron travels in tissue for a short distance (typically less than 1 mm, but dependent on the isotope^[9]), during which time it loses kinetic energy, until it decelerates to a point where it can interact with an electron.^[10] The encounter annihilates both electron and positron, producing a pair of annihilation (gamma) photons moving in approximately opposite directions. These are detected when they reach a scintillator in the scanning device, creating a burst of light which is detected by photomultiplier tubes or silicon avalanche photodiodes (Si APD). The technique depends on simultaneous or coincident detection of the pair of photons moving in approximately opposite direction (it would be exactly opposite in their center of mass frame, but the scanner has no way to know this, and so has a built-in slight direction-error tolerance). Photons that do not arrive in temporal "pairs" (i.e. within a timing-window of a few nanoseconds) are ignored.

Localization of the positron annihilation event

The most significant fraction of electron-positron decays result in two 511 keV gamma photons being emitted at almost 180 degrees to each other; hence it is possible to localize their source along a straight line of coincidence (also called formally the **line of response** or **LOR**). In practice the LOR has a finite width as the emitted photons are not exactly 180 degrees apart. If the resolving time of the detectors is less than 500 picoseconds rather than about 10 nanoseconds, it is possible to localize the event to a segment of a chord, whose length is determined by the detector timing resolution. As the timing resolution improves, the signal-to-noise ratio (SNR) of the image will improve, requiring fewer events to achieve the same image quality. This technology is not yet common, but it is available on

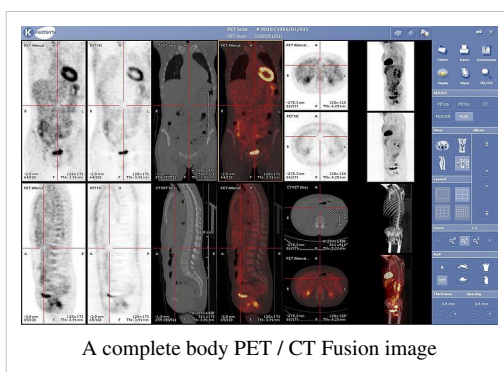


some new systems.^[11]

Image reconstruction using coincidence statistics

More commonly, a technique much like the reconstruction of computed tomography (CT) and single photon emission computed tomography (SPECT) data is used, although the data set collected in PET is much poorer than CT, so reconstruction techniques are more difficult (see Image reconstruction of PET).

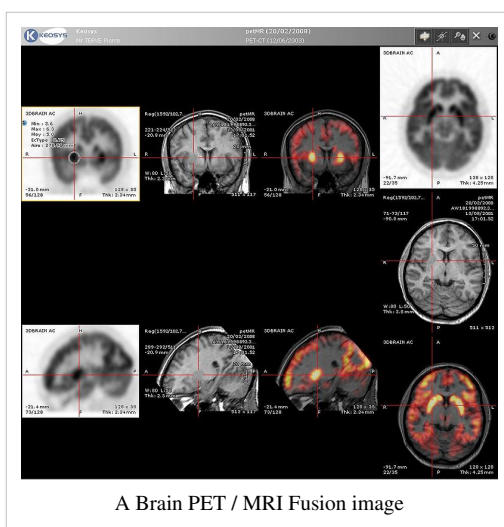
Using statistics collected from tens-of-thousands of coincidence events, a set of simultaneous equations for the total activity of each parcel of tissue along many LORs can be solved by a number of techniques, and thus a map of radioactivities as a function of location for parcels or bits of tissue (also called voxels), may be constructed and plotted. The resulting map shows the tissues in which the molecular tracer has become concentrated, and can be interpreted by a nuclear medicine physician or radiologist in the context of the patient's diagnosis and treatment plan.



Combination of PET with CT or MRI

PET scans are increasingly read alongside CT or magnetic resonance imaging (MRI) scans, the combination ("co-registration") giving both anatomic and metabolic information (i.e., what the structure is, and what it is doing biochemically). Because PET imaging is most useful in combination with anatomical imaging, such as CT, modern PET scanners are now available with integrated high-end multi-detector-row CT scanners. Because the two scans can be performed in immediate sequence during the same session, with the patient not changing position between the two types of scans, the two sets of images are more-precisely registered, so that areas of abnormality on the PET imaging can be more perfectly correlated with anatomy on the CT images. This is very useful in showing detailed views of moving organs or structures with higher anatomical variation, which is more common outside the brain.

At the Jülich Institute of Neurosciences and Biophysics, the world's largest PET/MRI device began operation in April 2009: a 9.4-tesla magnetic resonance tomograph (MRT) combined with a positron emission tomograph (PET). Presently, only the head and brain can be imaged at these high magnetic field strengths.^[12]



Radionuclides

Radionuclides used in PET scanning are typically isotopes with short half lives such as carbon-11 (~20 min), nitrogen-13 (~10 min), oxygen-15 (~2 min), and fluorine-18 (~110 min). These radionuclides are incorporated either into compounds normally used by the body such as glucose (or glucose analogues), water or ammonia, or into molecules that bind to receptors or other sites of drug action. Such labelled compounds are known as radiotracers. It is important to recognize that PET technology can be used to trace the biologic pathway of any compound in living humans (and many other species as well), provided it can be radiolabeled with a PET isotope. Thus the specific processes that can be probed with PET are virtually limitless, and radiotracers for new target molecules and processes are being synthesized all the time; as of this writing there are already dozens in clinical use and hundreds

applied in research. Presently, however, by far the most commonly used radiotracer in clinical PET scanning is FDG, an analogue of glucose that is labeled with fluorine-18.

Due to the short half lives of most radioisotopes, the radiotracers must be produced using a cyclotron in close proximity to the PET imaging facility. The half life of fluorine-18 is long enough that radiotracers labeled with fluorine-18 can be manufactured commercially at offsite locations and shipped to imaging centers.

Limitations

The minimization of radiation dose to the subject is an attractive feature of the use of short-lived radionuclides. Besides its established role as a diagnostic technique, PET has an expanding role as a method to assess the response to therapy, in particular, cancer therapy,^[13] where the risk to the patient from lack of knowledge about disease progress is much greater than the risk from the test radiation.

Limitations to the widespread use of PET arise from the high costs of cyclotrons needed to produce the short-lived radionuclides for PET scanning and the need for specially adapted on-site chemical synthesis apparatus to produce the radiopharmaceuticals. Few hospitals and universities are capable of maintaining such systems, and most clinical PET is supported by third-party suppliers of radiotracers which can supply many sites simultaneously. This limitation restricts clinical PET primarily to the use of tracers labelled with fluorine-18, which has a half life of 110 minutes and can be transported a reasonable distance before use, or to rubidium-82, which can be created in a portable generator and is used for myocardial perfusion studies. Nevertheless, in recent years a few on-site cyclotrons with integrated shielding and hot labs have begun to accompany PET units to remote hospitals. The presence of the small on-site cyclotron promises to expand in the future as the cyclotrons shrink in response to the high cost of isotope transportation to remote PET machines^[14]

Because the half-life of fluorine-18 is about two hours, the prepared dose of a radiopharmaceutical bearing this radionuclide will undergo multiple half-lives of decay during the working day. This necessitates frequent recalibration of the remaining dose (determination of activity per unit volume) and careful planning with respect to patient scheduling.

Image reconstruction

The raw data collected by a PET scanner are a list of 'coincidence events' representing near-simultaneous detection (typically, within a window of 6 to 12 nanoseconds of each other) of annihilation photons by a pair of detectors. Each coincidence event represents a line in space connecting the two detectors along which the positron emission occurred. Modern systems with a higher time resolution (roughly 3 nanoseconds) also use a technique (called "Time-of-flight") where they more precisely decide the difference in time between the detection of the two photons and can thus localize the point of origin of the annihilation event between the two detectors to within 10 cm.

Coincidence events can be grouped into projection images, called sinograms. The sinograms are sorted by the angle of each view and tilt (for 3D images). The sinogram images are analogous to the projections captured by computed tomography (CT) scanners, and can be reconstructed in a similar way. However, the statistics of the data are much worse than those obtained through transmission tomography. A normal PET data set has millions of counts for the whole acquisition, while the CT can reach a few billion counts. As such, PET data suffer from scatter and random events much more dramatically than CT data does.

In practice, considerable pre-processing of the data is required - correction for random coincidences, estimation and subtraction of scattered photons, detector dead-time correction (after the detection of a photon, the detector must "cool down" again) and detector-sensitivity correction (for both inherent detector sensitivity and changes in sensitivity due to angle of incidence).

Filtered back projection (FBP) has been frequently used to reconstruct images from the projections. This algorithm has the advantage of being simple while having a low requirement for computing resources. However, shot noise in the raw data is prominent in the reconstructed images and areas of high tracer uptake tend to form streaks across the

image. Also, FBP treats the data deterministically - it does not account for the inherent randomness associated with PET data, thus requiring all the pre-reconstruction corrections described above.

Iterative expectation-maximization algorithms are now the preferred method of reconstruction. These algorithms compute an estimate of the likely distribution of annihilation events that led to the measured data, based on statistical principles. The advantage is a better noise profile and resistance to the streak artifacts common with FBP, but the disadvantage is higher computer resource requirements.

Attenuation correction: As different LORs must traverse different thicknesses of tissue, the photons are attenuated differentially. The result is that structures deep in the body are reconstructed as having falsely low tracer uptake. Contemporary scanners can estimate attenuation using integrated x-ray CT equipment, however earlier equipment offered a crude form of CT using a gamma ray (positron emitting) source and the PET detectors.

While attenuation-corrected images are generally more faithful representations, the correction process is itself susceptible to significant artifacts. As a result, both corrected and uncorrected images are always reconstructed and read together.

2D/3D reconstruction: Early PET scanners had only a single ring of detectors, hence the acquisition of data and subsequent reconstruction was restricted to a single transverse plane. More modern scanners now include multiple rings, essentially forming a cylinder of detectors.

There are two approaches to reconstructing data from such a scanner: 1) treat each ring as a separate entity, so that only coincidences within a ring are detected, the image from each ring can then be reconstructed individually (2D reconstruction), or 2) allow coincidences to be detected between rings as well as within rings, then reconstruct the entire volume together (3D).

3D techniques have better sensitivity (because more coincidences are detected and used) and therefore less noise, but are more sensitive to the effects of scatter and random coincidences, as well as requiring correspondingly greater computer resources. The advent of sub-nanosecond timing resolution detectors affords better random coincidence rejection, thus favoring 3D image reconstruction.

Applications

PET is both a medical and research tool. It is used heavily in clinical oncology (medical imaging of tumors and the search for metastases), and for clinical diagnosis of certain diffuse brain diseases such as those causing various types of dementias. PET is also an important research tool to map normal human brain and heart function.

PET is also used in pre-clinical studies using animals, where it allows repeated investigations into the same subjects. This is particularly valuable in cancer research, as it results in an increase in the statistical quality of the data (subjects can act as their own control) and substantially reduces the numbers of animals required for a given study.

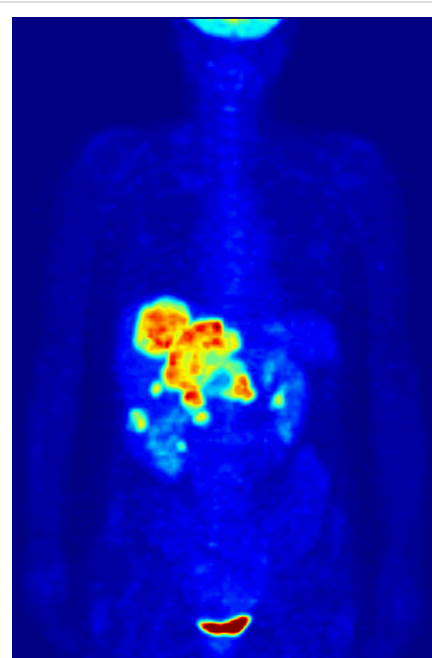
Alternative methods of scanning include x-ray computed tomography (CT), magnetic resonance imaging (MRI) and functional magnetic resonance imaging (fMRI), ultrasound and single photon emission computed tomography (SPECT).

While some imaging scans such as CT and MRI isolate organic anatomic changes in the body, PET and SPECT are capable of detecting areas of molecular biology detail (even prior to anatomic change). PET scanning does this using radiolabelled molecular probes that have different rates of uptake depending on the type and function of tissue involved. Changing of regional blood flow in various anatomic structures (as a measure of the injected positron emitter) can be visualized and relatively quantified with a PET scan.

PET imaging is best performed using a dedicated PET scanner. However, it is possible to acquire PET images using a conventional dual-head gamma camera fitted with a coincidence detector. The quality of gamma-camera PET is considerably lower, and acquisition is slower. However, for institutions with low demand for PET, this may allow on-site imaging, instead of referring patients to another center, or relying on a visit by a mobile scanner.

PET is a valuable technique for some diseases and disorders, because it is possible to target the radio-chemicals used for particular bodily functions.

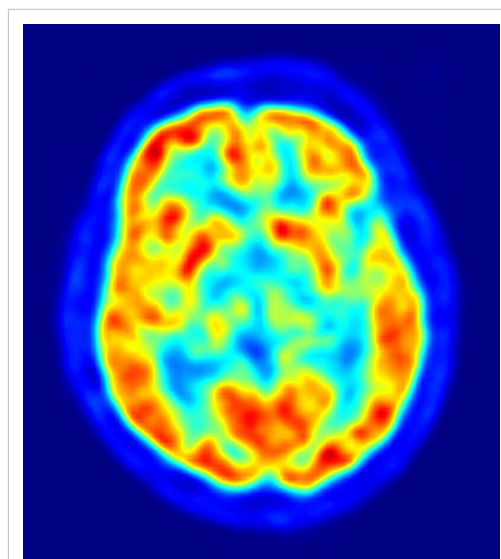
1. **Oncology:** PET scanning with the tracer fluorine-18 (F-18) fluorodeoxyglucose (FDG), called FDG-PET, is widely used in clinical oncology. This tracer is a glucose analog that is taken up by glucose-using cells and phosphorylated by hexokinase (whose mitochondrial form is greatly elevated in rapidly growing malignant tumours). A typical dose of FDG used in an oncological scan is 200-400 MBq for an adult human. Because the oxygen atom which is replaced by F-18 to generate FDG is required for the next step in glucose metabolism in all cells, no further reactions occur in FDG. Furthermore, most tissues (with the notable exception of liver and kidneys) cannot remove the phosphate added by hexokinase. This means that FDG is trapped in any cell which takes it up, until it decays, since phosphorylated sugars, due to their ionic charge, cannot exit from the cell. This results in intense radiolabeling of tissues with high glucose uptake, such as the brain, the liver, and most cancers. As a result, FDG-PET can be used for diagnosis, staging, and monitoring treatment of cancers, particularly in Hodgkin's lymphoma, non-Hodgkin lymphoma, and lung cancer. Many other types of solid tumors will be found to be very highly labeled on a case-by-case basis—a fact which becomes especially useful in searching for tumor metastasis, or for recurrence after a known highly active primary tumor is removed. Because individual PET scans are more expensive than "conventional" imaging with computed tomography (CT) and magnetic resonance imaging (MRI), expansion of FDG-PET in cost-constrained health services will depend on proper health



Maximum intensity projection (MIP) of a F-18 FDG wholebody PET acquisition; liver metastases of a colorectal tumor are clearly visible within the abdominal region of the image. Normal physiological isotope uptake is seen in the brain, renal collection systems and bladder. In this animation, it is important to view the subject as rotating clockwise (note liver position).

technology assessment; this problem is a difficult one because structural and functional imaging often cannot be directly compared, as they provide different information. Oncology scans using FDG make up over 90% of all PET scans in current practice.

Neurology: PET neuroimaging is based on an assumption that areas of high radioactivity are associated with brain activity. What is actually measured indirectly is the flow of blood to different parts of the brain, which is generally believed to be correlated, and has been measured using the tracer oxygen-15. However, because of its 2-minute half-life O-15 must be piped directly from a medical cyclotron for such uses, and this is difficult. In practice, since the brain is normally a rapid user of glucose, and since brain pathologies such as Alzheimer's disease greatly decrease brain metabolism of both glucose and oxygen in tandem, standard FDG-PET of the brain, which measures regional glucose use, may also be successfully used to differentiate Alzheimer's disease from other dementing processes, and also to make early diagnosis of Alzheimer's disease. The advantage of FDG-PET for these uses is its much wider availability. PET imaging with FDG can also be used for localization of seizure focus: A seizure focus will appear



PET scan of the human brain.

as hypometabolic during an interictal scan. Several radiotracers (i.e. radioligands) have been developed for PET that are ligands for specific neuroreceptor subtypes such as [^{11}C] raclopride and [^{18}F] fallypride for dopamine D2/D3 receptors, [^{11}C]McN 5652 and [^{11}C]DASB for serotonin transporters, or enzyme substrates (e.g. 6-FDOPA for the AADC enzyme). These agents permit the visualization of neuroreceptor pools in the context of a plurality of neuropsychiatric and neurologic illnesses. A novel probe developed at the University of Pittsburgh termed PIB (Pittsburgh compound B) permits the visualization of amyloid plaques in the brains of Alzheimer's patients. This technology could assist clinicians in making a positive clinical diagnosis of AD pre-mortem and aid in the development of novel anti-amyloid therapies. [^{11}C]PMP (N-[^{11}C]methylpiperidin-4-yl propionate) is a novel radiopharmaceutical used in PET imaging to determine the activity of the acetylcholinergic neurotransmitter system by acting as a substrate for acetylcholinesterase. Post-mortem examination of AD patients have shown decreased levels of acetylcholinesterase. [^{11}C]PMP is used to map the acetylcholinesterase activity in the brain which could allow for pre-mortem diagnosis of AD and help to monitor AD treatments.^[15] Avid Radiopharmaceuticals of Philadelphia has developed a compound called 18F-AV-45 that uses the longer-lasting radionuclide fluorine-18 to detect amyloid plaques using PET scans.^[16]

3. Cardiology, atherosclerosis and vascular disease study: In clinical cardiology, FDG-PET can identify so-called "hibernating myocardium", but its cost-effectiveness in this role versus SPECT is unclear. Recently, a role has been suggested for FDG-PET imaging of atherosclerosis to detect patients at risk of stroke [17].
4. Neuropsychology / Cognitive neuroscience: To examine links between specific psychological processes or disorders and brain activity.
5. Psychiatry: Numerous compounds that bind selectively to neuroreceptors of interest in biological psychiatry have been radiolabeled with C-11 or F-18. Radioligands that bind to dopamine receptors (D1,D2, reuptake transporter), serotonin receptors (5HT1A, 5HT2A, reuptake transporter) opioid receptors (μ) and other sites have been used successfully in studies with human subjects. Studies have been performed examining the state of these receptors in patients compared to healthy controls in schizophrenia, substance abuse, mood disorders and other psychiatric conditions.
6. Pharmacology: In pre-clinical trials, it is possible to radiolabel a new drug and inject it into animals. Such scans are referred to as biodistribution studies. The uptake of the drug, the tissues in which it concentrates, and its

eventual elimination, can be monitored far more quickly and cost effectively than the older technique of killing and dissecting the animals to discover the same information. Much more commonly, however, drug occupancy at a purported site of action can be inferred indirectly by competition studies between unlabeled drug and radiolabeled compounds known apriori to bind with specificity to the site. A single radioligand can be used this way to test many potential drug candidates for the same target. A related technique involves scanning with radioligands that compete with an endogenous (naturally occurring) substance at a given receptor to demonstrate that a drug causes the release of the natural substance.

7. PET technology for small animal imaging: A miniature PET tomograph has been constructed that is small enough for a fully conscious and mobile rat to wear on its head while walking around.^[18] This RatCAP (Rat Conscious Animal PET) allows animals to be scanned without the confounding effects of anesthesia. PET scanners designed specifically for imaging rodents or small primates are marketed for academic and pharmaceutical research.
8. Musculo-Skeletal Imaging: PET has been shown to be a feasible technique for studying skeletal muscles during exercises like walking.^[19] One of the main advantages of using PET is that it can also provide muscle activation data about deeper lying muscles such as the vastus intermedius and the gluteus minimus, as compared to other muscle studying techniques like Electromyography, which can only be used on superficial muscles (i.e. directly under the skin). A clear disadvantage, however, is that PET provides no timing information about muscle activation, because it has to be measured after the exercise is completed. This is due to the time it takes for FDG to accumulate in the activated muscles.

Safety

PET scanning is non-invasive, but it does involve exposure to ionizing radiation. The total dose of radiation is not insignificant, usually around 5–7 mSv. However, in modern practice, a combined PET/CT scan is almost always performed, and for PET/CT scanning, the radiation exposure may be substantial - around 23–26 mSv (for a 70 kg person - dose is likely to be higher for higher body weights).^[20] When compared to the classification level for radiation workers in the UK, of 6 mSv it can be seen that PET scans need proper justification. This can also be compared to 2.2 mSv average annual background radiation in the UK, 0.02 mSv for a chest x-ray and 6.5 - 8 mSv for a CT scan of the chest, according to the Chest Journal and ICRP.^[21] ^[22] A policy change suggested by the IFALPA member associations in year 1999 mentioned that an aircrew member is likely to receive a radiation dose of 4–9 mSv per year.^[23]

See also

- Diffuse optical imaging
- Hot cell (Equipment used to produce the radiopharmaceuticals used in PET)
- Molecular Imaging

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Further reading

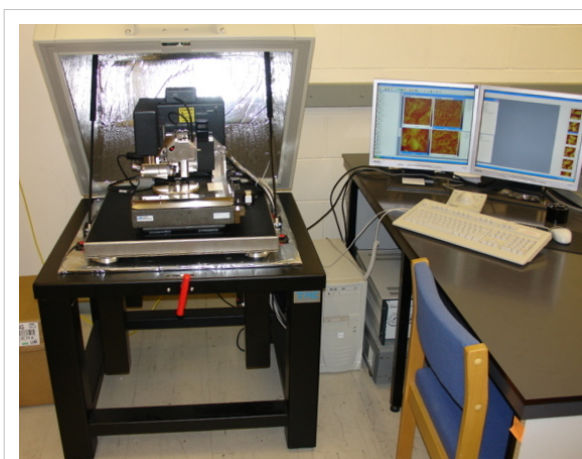
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External links

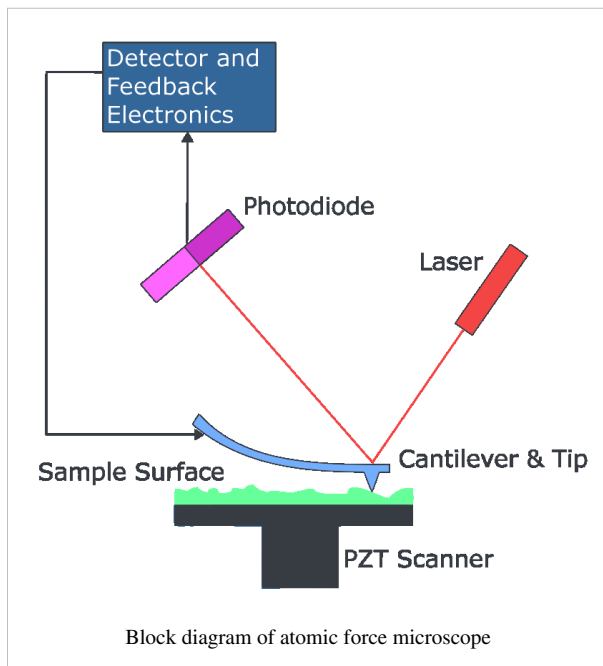
- PET Images (http://rad.usuhs.edu/medpix/master.php3?mode=image_finder&action=search&srchstr=&srch_type=all&labels=&details=2&no_filter=2&plane_id=&capt_id=-4&filter_m=modality&filter_o=&acr_pre=&filter_p=&acr_post=#top) Search MedPix(r)
- Seeing is believing: In vivo functional real-time imaging of transplanted islets using positron emission tomography (PET)(a protocol) (http://www.natureprotocols.com/2006/12/21/seeing_is_believing_in_vivo_fu_1.php), Nature Protocols, from Nature Medicine - 12, 1423 - 1428 (2006).
- The nuclear medicine and molecular medicine podcast (<http://nucast.com>) - Podcast
- Positron Emission Particle Tracking (<http://www.np.ph.bham.ac.uk/pic/pept.htm>) (PEPT) - engineering analysis tool based on PET that is able to track single particles in 3D within mixing systems or fluidised beds. Developed at the University of Birmingham, UK.
- CMS coverage of PET scans (http://www.hematologytimes.com/ht/p_article.do?id=948)
- PET-CT atlas Harvard Medical School (<http://www.med.harvard.edu/JPNM/chetan/>)

Atomic force microscope

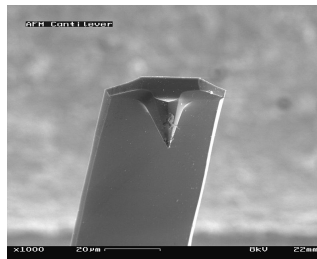
Atomic force microscopy (AFM) or scanning force microscopy (SFM) is a very high-resolution type of scanning probe microscopy, with demonstrated resolution on the order of fractions of a nanometer, more than 1000 times better than the optical diffraction limit. The precursor to the AFM, the scanning tunneling microscope, was developed by Gerd Binnig and Heinrich Rohrer in the early 1980s at IBM Research - Zurich, a development that earned them the Nobel Prize for Physics in 1986. Binnig, Quate and Gerber invented the first atomic force microscope (also abbreviated as AFM) in 1986. The first commercially available atomic force microscope was introduced in 1989. The AFM is one of the foremost tools for imaging, measuring, and manipulating matter at the nanoscale. The information is gathered by "feeling" the surface with a mechanical probe. Piezoelectric elements that facilitate tiny but accurate and precise movements on (electronic) command enable the very precise scanning. In some variations, electric potentials can also be scanned using conducting cantilevers. In newer more advanced versions, currents can even be passed through the tip to probe the electrical conductivity or transport of the underlying surface, but this is much more challenging with very few research groups reporting reliable data.



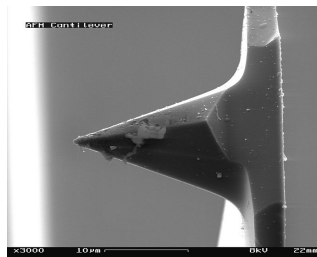
A commercial AFM setup



Basic principles



Electron micrograph of a used AFM cantilever image width ~100 micrometers...



and ~30 micrometers

The AFM consists of a cantilever with a sharp tip (probe) at its end that is used to scan the specimen surface. The cantilever is typically silicon or silicon nitride with a tip radius of curvature on the order of nanometers. When the tip is brought into proximity of a sample surface, forces between the tip and the sample lead to a deflection of the cantilever according to Hooke's law. Depending on the situation, forces that are measured in AFM include mechanical contact force, van der Waals forces, capillary forces, chemical bonding, electrostatic forces, magnetic forces (see magnetic force microscope, MFM), Casimir forces, solvation forces, etc. Along with force, additional quantities may simultaneously be measured through the use of specialized types of probe (see scanning thermal microscopy, scanning joule expansion microscopy, photothermal microspectroscopy, etc.). Typically, the deflection is measured using a laser spot reflected from the top surface of the cantilever into an array of photodiodes. Other methods that are used include optical interferometry, capacitive sensing or piezoresistive AFM cantilevers. These

cantilevers are fabricated with piezoresistive elements that act as a strain gauge. Using a Wheatstone bridge, strain in the AFM cantilever due to deflection can be measured, but this method is not as sensitive as laser deflection or interferometry.

If the tip was scanned at a constant height, a risk would exist that the tip collides with the surface, causing damage. Hence, in most cases a feedback mechanism is employed to adjust the tip-to-sample distance to maintain a constant force between the tip and the sample. Traditionally, the sample is mounted on a piezoelectric tube, that can move the sample in the z direction for maintaining a constant force, and the x and y directions for scanning the sample. Alternatively a 'tripod' configuration of three piezo crystals may be employed, with each responsible for scanning in the x, y and z directions. This eliminates some of the distortion effects seen with a tube scanner. In newer designs, the tip is mounted on a vertical piezo scanner while the sample is being scanned in X and Y using another piezo block. The resulting map of the area $s = f(x, y)$ represents the topography of the sample.

The AFM can be operated in a number of modes, depending on the application. In general, possible imaging modes are divided into static (also called *contact*) modes and a variety of dynamic (or non-contact) modes where the cantilever is vibrated.

Imaging modes

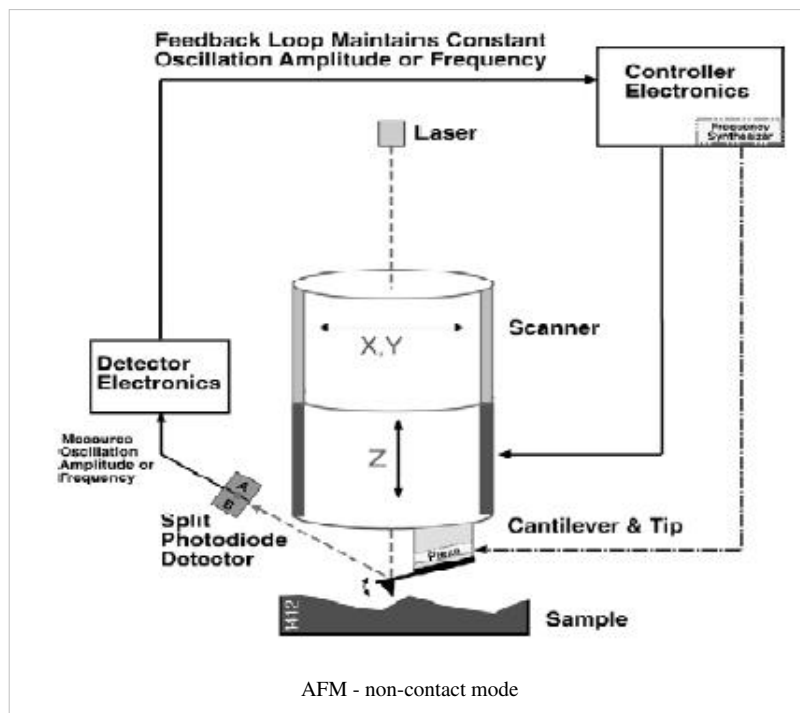
The primary modes of operation for an AFM are static mode and dynamic mode. In static mode, the cantilever is "dragged" across the surface of the sample and the contours of the surface are measured directly using the deflection of the cantilever. In the dynamic mode, the cantilever is externally oscillated at or close to its fundamental resonance frequency or a harmonic. The oscillation amplitude, phase and resonance frequency are modified by tip-sample interaction forces. These changes in oscillation with respect to the external reference oscillation provide information about the sample's characteristics.

Contact mode

In the static mode operation, the static tip deflection is used as a feedback signal. Because the measurement of a static signal is prone to noise and drift, low stiffness cantilevers are used to boost the deflection signal. However, close to the surface of the sample, attractive forces can be quite strong, causing the tip to "snap-in" to the surface. Thus static mode AFM is almost always done in contact where the overall force is repulsive. Consequently, this technique is typically called "contact mode". In contact mode, the force between the tip and the surface is kept constant during scanning by maintaining a constant deflection.

Non-contact mode

In this mode, the tip of the cantilever does not contact the sample surface. The cantilever is instead oscillated at a frequency slightly above its resonance frequency where the amplitude of oscillation is typically a few nanometers (<10 nm). The van der Waals forces, which are strongest from 1 nm to 10 nm above the surface, or any other long range force which extends above the surface acts to decrease the resonance frequency of the cantilever. This decrease in resonance frequency combined with the feedback loop system maintains a constant oscillation amplitude or frequency by adjusting the average tip-to-sample distance. Measuring the tip-to-sample distance at each (x,y) data point allows the scanning software to construct a topographic image of the sample surface.



Non-contact mode AFM does not suffer from tip or sample degradation effects that are sometimes observed after taking numerous scans with contact AFM. This makes non-contact AFM preferable to contact AFM for measuring soft samples. In the case of rigid samples, contact and non-contact images may look the same. However, if a few monolayers of adsorbed fluid are lying on the surface of a rigid sample, the images may look quite different. An AFM operating in contact mode will penetrate the liquid layer to image the underlying surface, whereas in non-contact mode an AFM will oscillate above the adsorbed fluid layer to image both the liquid and surface.

Schemes for dynamic mode operation include frequency modulation and the more common amplitude modulation. In frequency modulation, changes in the oscillation frequency provide information about tip-sample interactions. Frequency can be measured with very high sensitivity and thus the frequency modulation mode allows for the use of very stiff cantilevers. Stiff cantilevers provide stability very close to the surface and, as a result, this technique was the first AFM technique to provide true atomic resolution in ultra-high vacuum conditions.^[1]

In amplitude modulation, changes in the oscillation amplitude or phase provide the feedback signal for imaging. In amplitude modulation, changes in the phase of oscillation can be used to discriminate between different types of materials on the surface. Amplitude modulation can be operated either in the non-contact or in the intermittent contact regime. In dynamic contact mode, the cantilever is oscillated such that the separation distance between the cantilever tip and the sample surface is modulated.

Amplitude modulation has also been used in the non-contact regime to image with atomic resolution by using very stiff cantilevers and small amplitudes in an ultra-high vacuum environment.

Tapping mode

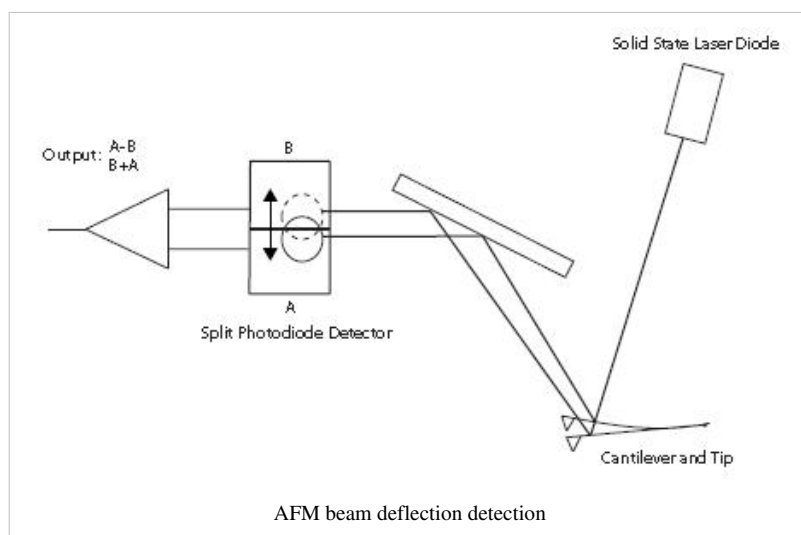
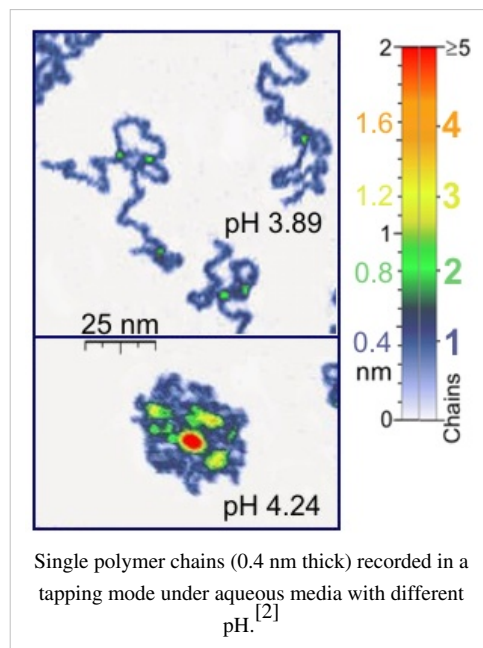
In ambient conditions, most samples develop a liquid meniscus layer. Because of this, keeping the probe tip close enough to the sample for short-range forces to become detectable while preventing the tip from sticking to the surface presents a major problem for non-contact dynamic mode in ambient conditions. Dynamic contact mode (also called intermittent contact or tapping mode) was developed to bypass this problem.^[3]

In *tapping mode*, the cantilever is driven to oscillate up and down at near its resonance frequency by a small piezoelectric element mounted in the AFM tip holder similar to non-contact mode. However, the amplitude of this oscillation is greater than 10 nm, typically 100 to 200 nm. Due to the interaction of forces acting on the cantilever when the tip comes close to the surface, Van der Waals force, dipole-dipole interaction, electrostatic forces, etc. cause the amplitude of this oscillation to decrease as the tip gets closer to the sample. An electronic servo uses the piezoelectric actuator to control the height of the cantilever above the sample. The servo adjusts the height to maintain a set cantilever oscillation amplitude as the cantilever is scanned over the sample. A *tapping AFM* image is therefore produced by imaging the force of the intermittent contacts of the tip with the sample surface.

This method of "tapping" lessens the damage done to the surface and the tip compared to the amount done in contact mode. Tapping mode is gentle enough even for the visualization of supported lipid bilayers or adsorbed single polymer molecules (for instance, 0.4 nm thick chains of synthetic polyelectrolytes) under liquid medium. With proper scanning parameters, the conformation of single molecules can remain unchanged for hours.^[2]

AFM cantilever deflection measurement

Laser light from a solid state diode is reflected off the back of the cantilever and collected by a position sensitive detector (PSD) consisting of two closely spaced photodiodes whose output signal is collected by a differential amplifier. Angular displacement of cantilever results in one photodiode collecting more light than the other photodiode, producing an output signal (the difference between the photodiode signals normalized by their sum) which is proportional to the deflection of the cantilever. It detects cantilever deflections <10 nm (thermal noise limited). A long beam path (several centimeters) amplifies changes in beam angle.



Force spectroscopy

Another major application of AFM (besides imaging) is force spectroscopy, the direct measurement of tip-sample interaction forces as a function of the gap between the tip and sample (the result of this measurement is called a force-distance curve). For this method, the AFM tip is extended towards and retracted from the surface as the deflection of the cantilever is monitored as a function of piezoelectric displacement. These measurements have been used to measure nanoscale contacts, atomic bonding, Van der Waals forces, and Casimir forces, dissolution forces in liquids and single molecule stretching and rupture forces.^[4] Furthermore, AFM was used to measure in aqueous environment dispersion force due to polymer adsorbed on the substrate.^[5] Forces of the order of a few piconewtons can now be routinely measured with a vertical distance resolution of better than 0.1 nanometers. Force spectroscopy can be performed with either static or dynamic modes. In dynamic modes, information about the cantilever vibration is monitored in addition to the static deflection.^[6]

Problems with the technique include no direct measurement of the tip-sample separation and the common need for low stiffness cantilevers which tend to 'snap' to the surface. The snap-in can be reduced by measuring in liquids or by using stiffer cantilevers, but in the latter case a more sensitive deflection sensor is needed. By applying a small dither to the tip, the stiffness (force gradient) of the bond can be measured as well.^[7]

Identification of individual surface atoms

The AFM can be used to image and manipulate atoms and structures on a variety of surfaces. The atom at the apex of the tip "senses" individual atoms on the underlying surface when it forms incipient chemical bonds with each atom. Because these chemical interactions subtly alter the tip's vibration frequency, they can be detected and mapped. This principle was used to distinguish between atoms of silicon, tin and lead on an alloy surface, by comparing these 'atomic fingerprints' to values obtained from large-scale density functional theory (DFT) simulations.^[8]

The trick is to first measure these forces precisely for each type of atom expected in the sample, and then to compare with forces given by DFT simulations. The team found that the tip interacted most strongly with silicon atoms, and interacted 23% and 41% less strongly with tin and lead atoms, respectively. Thus, each different type of atom can be identified in the matrix as the tip is moved across the surface.

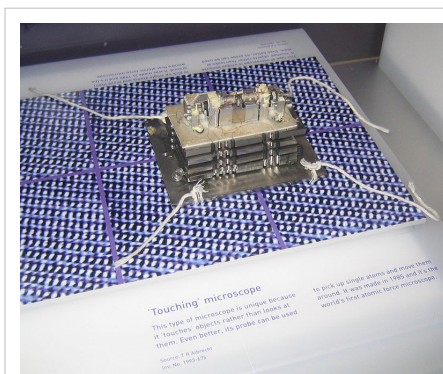
Such a technique has been used now in biology and extended recently to cell biology. Forces corresponding to (i) the unbinding of receptor ligand couples (ii) unfolding of proteins (iii) cell adhesion at single cell scale have been gathered.

Advantages and disadvantages

Just like any other tool, an AFM's usefulness has limitations. When determining whether or not analyzing a sample with an AFM is appropriate, there are various advantages and disadvantages that must be considered.

Advantages

AFM has several advantages over the scanning electron microscope (SEM). Unlike the electron microscope which provides a two-dimensional projection or a two-dimensional image of a sample, the AFM provides a three-dimensional surface profile. Additionally,



The first atomic force microscope

samples viewed by AFM do not require any special treatments (such as metal/carbon coatings) that would irreversibly change or damage the sample. While an electron microscope needs an expensive vacuum environment for proper operation, most AFM modes can work perfectly well in ambient air or even a liquid environment. This makes it possible to study biological macromolecules and even living organisms. In principle, AFM can provide higher resolution than SEM. It has been shown to give true atomic resolution in ultra-high vacuum (UHV) and, more recently, in liquid environments. High resolution AFM is comparable in resolution to scanning tunneling microscopy and transmission electron microscopy.

Disadvantages

A disadvantage of AFM compared with the scanning electron microscope (SEM) is the single scan image size. In one pass, the SEM can image an area on the order of square millimeters with a depth of field on the order of millimeters. Whereas the AFM can only image a maximum height on the order of 10-20 micrometers and a maximum scanning area of about 150×150 micrometers. One method of improving the scanned area size for AFM is by using parallel probes in a fashion similar to that of millipede data storage.

The scanning speed of an AFM is also a limitation. Traditionally, an AFM cannot scan images as fast as a SEM, requiring several minutes for a typical scan, while a SEM is capable of scanning at near real-time, although at relatively low quality. The relatively slow rate of scanning during AFM imaging often leads to thermal drift in the image^{[9] [10]} making the AFM microscope less suited for measuring accurate distances between topographical features on the image. However, several fast-acting designs^{[11] [12]} were suggested to increase microscope scanning productivity including what is being termed videoAFM (reasonable quality images are being obtained with videoAFM at video rate: faster than the average SEM). To eliminate image distortions induced by thermal drift, several methods have been introduced.^{[9] [10]}

AFM images can also be affected by hysteresis of the piezoelectric material^[13] and cross-talk between the *x*, *y*, *z* axes that may require software enhancement and filtering. Such filtering could "flatten" out real topographical features. However, newer AFMs utilize closed-loop scanners which practically eliminate these problems. Some AFMs also use separated orthogonal scanners (as opposed to a single tube) which also serve to eliminate part of the cross-talk problems.

As with any other imaging technique, there is the possibility of image artifacts, which could be induced by an unsuitable tip, a poor operating environment, or even by the sample itself. These image artifacts are unavoidable however, their occurrence and effect on results can be reduced through various methods.

Due to the nature of AFM probes, they cannot normally measure steep walls or overhangs. Specially made cantilevers and AFMs can be used to modulate the probe sideways as well as up and down (as with dynamic contact and non-contact modes) to measure sidewalls, at the cost of more expensive cantilevers, lower lateral resolution and additional artifacts.

Piezoelectric scanners

AFM scanners are made from piezoelectric material, which expands and contracts proportionally to an applied voltage. Whether they elongate or contract depends upon the polarity of the voltage applied. The scanner is constructed by combining independently operated piezo electrodes for *X*, *Y*, and *Z* into a single tube, forming a scanner which can manipulate samples and probes with extreme precision in 3 dimensions.

Scanners are characterized by their sensitivity which is the ratio of piezo movement to piezo voltage, i.e., by how much the piezo material extends or contracts per applied volt. Because of differences in material or size, the sensitivity varies from scanner to scanner. Sensitivity varies non-linearly with respect to scan size. Piezo scanners exhibit more sensitivity at the end than at the beginning of a scan. This causes the forward and reverse scans to behave differently and display hysteresis^[13] between the two scan directions. This can be corrected by applying a

non-linear voltage to the piezo electrodes to cause linear scanner movement and calibrating the scanner accordingly.^[13]

The sensitivity of piezoelectric materials decreases exponentially with time. This causes most of the change in sensitivity to occur in the initial stages of the scanner's life. Piezoelectric scanners are run for approximately 48 hours before they are shipped from the factory so that they are past the point where they may have large changes in sensitivity. As the scanner ages, the sensitivity will change less with time and the scanner would seldom require recalibration.^[14]

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External links

- ME 597/PHYS 570: Fundamentals of Atomic Force Microscopy (<http://nanohub.org/resources/7320>)
- DoITPoMS Teaching and Learning Package - Atomic Force Microscopy (<http://www.doitpoms.ac.uk/tlplib/afm/index.php>)
- SPM gallery: surface scans, collages, artworks, desktop wallpapers (<http://www.nanoworld.org/homepages/lapshin/gallery.htm>)

Further reading

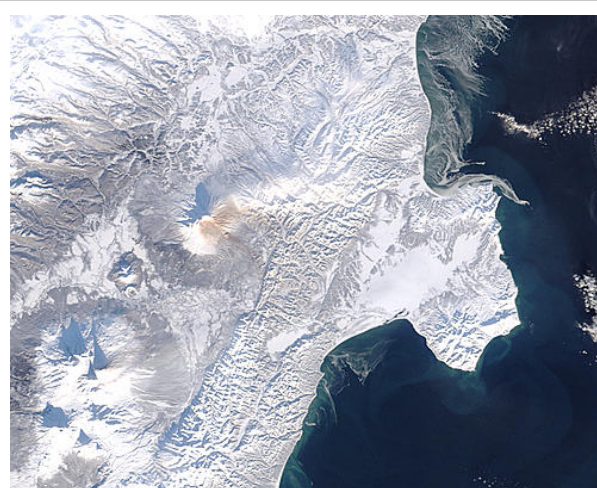
- SPM - Scanning Probe Microscopy Website (<http://www.mobot.org/jwcross/spm/>)
- Atomic Force Microscopy resource library (<http://www.afmuniversity.org>)
- R. W. Carpick and M. Salmeron, Scratching the surface: Fundamental investigations of tribology with atomic force microscopy (<http://dx.doi.org/10.1021/cr960068q>), Chemical Reviews, vol. 97, iss. 4, pp. 1163–1194 (2007).

Raman Microscopy

Raman microscope begins with a standard optical microscope, and adds an excitation laser, a monochromator, and an optical sensitive detector such as a charge-coupled device (CCD), or photomultiplier tube, (PMT)), and has been implemented for Raman spectroscopy in direct chemical imaging, the whole field of view on 3D sample.

Imaging spectroscopy

Imaging spectroscopy (also **spectral imaging**, chemical imaging, or microspectroscopy) is similar to color photography, but each pixel acquires many bands of light intensity data from the spectrum, instead of just the three bands of the RGB color model. More precisely, it is the simultaneous acquisition of spatially coregistered images in many spectrally contiguous bands.



Ash plumes on Kamchatka Peninsula, eastern Russia. A MODIS image.

Some spectral images contain only a few image planes of spectral data, while others are better thought of as full spectra at every location in the image. For example, solar physicists use the spectroheliograph, to make images of the Sun built up by scanning the slit of a spectrograph, to study the behavior of surface features on the Sun; such a spectroheliogram may have a spectral resolution of over 100,000 ($\lambda/\Delta\lambda$) and be used to measure local motion (via the Doppler shift) and even the magnetic field (via the Zeeman splitting or Hanle effect) at each location in the image plane. The multispectral images collected by the Opportunity rover, in contrast, have only four wavelength

bands and hence are only a little more than 3-color images.

To be scientifically useful, such measurement should be done using an internationally recognized system of units.

One example application is spectral geophysical imaging, which allows quantitative and qualitative characterization of the surface and of the atmosphere, using geometrically coherent spectrodirectional radiometric measurements. These measurements can then be used for the unambiguous direct and indirect identification of surface materials and atmospheric trace gases, the measurement of their relative concentrations, subsequently the assignment of the proportional contribution of mixed pixel signals (e.g., the spectral unmixing problem), the derivation of their spatial distribution (mapping problem), and finally their study over time (multi-temporal analysis). The Moon Mineralogy Mapper on Chandrayaan-1 was an imaging spectrometer.^[1]

Background

About 300 years ago, in 1704, Sir Isaac Newton published in his 'Treatise of Light' (Newton, 1704) the concept of dispersion of light. He demonstrated that white light could be split up into component colours by means of a prism, and found that each pure colour is characterized by a specific refrangibility. The corpuscular theory by Newton was gradually succeeded over time by the wave theory. Consequently, the substantial summary of past experiences performed by Maxwell (1873), resulted in his equations of electromagnetic waves. But it was not until the 19th century that the quantitative measurement of dispersed light was recognized and standardized.

A major contribution was Fraunhofer's discovery of the dark lines in the solar spectrum (Fraunhofer, 1817); and their interpretation as absorption lines on the basis of experiments by Bunsen and Kirchhoff (1863). The term "spectroscopy" was first used in the late 19th century and provides the empirical foundations for atomic and molecular physics (Born & Wolf, 1999). Significant achievements in imaging spectroscopy are attributed to airborne instruments, particularly arising in the early 1980s and 1990s (Goetz et al., 1985; Vane et al., 1984). However, it was not until 1999 that the first imaging spectrometer was launched in space (the NASA Moderate-resolution Imaging Spectroradiometer, or MODIS).

Terminology and definitions evolve over time. At one time, >10 spectral bands sufficed to justify the term "imaging spectrometer" but presently the term is seldom defined by a total minimum number of spectral bands, rather by a contiguous (or redundant) statement of spectral bands.

The term hyperspectral imaging is sometimes used interchangeably with imaging spectroscopy. Due to its heavy use in military related applications, the civil world has established a slight preference for using the term imaging spectroscopy.

Unmixing

Hyperspectral data is often used to determine what materials are present in a scene. Materials of interest could include roadways, vegetation, and specific targets (i.e. pollutants, hazardous materials, etc.). Trivially, each pixel of a hyperspectral image could be compared to a material database to determine the type of material making up the pixel. However, many hyperspectral imaging platforms have low resolution (>5m per pixel) causing each pixel to be a mixture of several materials. The process of unmixing one of these 'mixed' pixels is called hyperspectral image unmixing or simply hyperspectral unmixing.

Models

A solution to hyperspectral unmixing is to reverse the mixing process. Generally, two models of mixing are assumed: linear and nonlinear. Linear mixing models the ground as being flat and incident sunlight on the ground causes the materials to radiate some amount of the incident energy back to the sensor. Each pixel then, is modeled as a linear sum of all the radiated energy curves of materials making up the pixel. Therefore, each material contributes to the sensor's observation in a positive linear fashion. Additionally, a conservation of energy constraint is often

observed thereby forcing the weights of the linear mixture to sum to one in addition to being positive. The model can be described mathematically as follows:

$$p = A * x$$

where p represents a pixel observed by the sensor, A is a matrix of material reflectance signatures (each signature is a column of the matrix), and x is the proportion of material present in the observed pixel. This type of model is also referred to as a simplex.

With x satisfying the two constraints: 1. Abundance Nonnegativity Constraint (ANC) - each element of x is positive. 2. Abundance Sum-to-one Constraint (ASC) - the elements of x must sum to one.

Non-linear mixing results from multiple scattering often due to non-flat surface such as buildings and vegetation.

Unmixing (Endmember Detection) Algorithms

There are many algorithms to unmix hyperspectral data each with their own strengths and weaknesses. Many algorithms assume that pure pixels (pixels which contain only one materials) are present in a scene. Some algorithms to perform unmixing are listed below:

- Pixel Purity Index (PPI) - Works by projecting each pixel onto one vector from a set of random vectors spanning the reflectance space. A pixel receives a score when it represent an extremum of all the projections. Pixels with the highest scores are deemed to be spectrally pure.
- NFINDR
- Gift Wrapping Algorithm
- Independent Component Analysis Endmember Extraction Algorithm (ICA-EEA) - Works by assuming that pure pixels occur independently than mixed pixels. Assumes pure pixels are present.
- Vertex Component Analysis (VCA) - Works on the fact that the affine transformation of a simplex is another simplex which helps to find hidden (folded) vertices of the simplex. Assumes pure pixels are present.
- Principal component analysis -(PCA) could also be used to determine endmembers, projection on principal axes could permit endmember selection [Smith,Johnson et Adams (1985), Bateson et Curtiss (1996)]
- Multi Endmembers Spatial Mixture Analysis (MESMA) based on the SMA algorithm

Non-linear unmixing algorithm also exist (support vector machines (SVM)) or Analytical Neural Network (ANN). Probabilistics methods have also been attempted to unmix pixel through Monte Carlo Unmixing (MCU) algorithm.

Abundance Maps

Once the fundamental materials of a scene are determined, it is often useful to construct an abundance map of each material which displays the fractional amount of material present at each pixel. Often linear programming is done to observed ANC and ASC.

Sensors

- AVIRIS — aircraft, (224 bands)
- Telops Hyper-Cam^[2] — Commercial infrared hyperspectral camera, ground-based or aircraft
- MODIS — on board EOS Terra and Aqua platforms
- MERIS — on board Envisat
- HyDice
- Hyperion — on board the Earth Observing 1 satellite

See also

- Remote sensing
- Hyperspectral
- Full Spectral Imaging
- List of Earth observation satellites
- Chemical Imaging
- Imaging spectrometer
- Infrared Microscopy

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External links

- About imaging spectroscopy (USGS): <http://speclab.cr.usgs.gov/aboutimsp.html>
 - Link to resources (OKSI): http://www.techexpo.com/WWW/opto-knowledge/IS_resources.html
 - Special Interest Group Imaging Spectroscopy (EARSeL): <http://www.op.dlr.de/dais/SIG-IS/SIG-IS.html>
 - Applications of Spectroscopic and Chemical Imaging in Research: <http://www3.imperial.ac.uk/vibrationalspectroscopyandchemicalimaging/research>
-

Chemical imaging

Chemical imaging (as quantitative - *chemical mapping*) is the analytical capability to create a visual image of components distribution from simultaneous measurement of spectra and spatial, time informations. ^{[1] [2]}

The main idea - for chemical imaging, the analyst may choose to take as many data spectrum measured at a particular chemical component in spatial location at time; this is useful for chemical identification and quantification. Alternatively, selecting an image plane at a particular data spectrum (PCA - multivariable data of wavelength, spatial location at time) can map the spatial distribution of sample components, provided that their spectral signatures are different at the selected data spectrum.

Software for chemical imaging is most specific and distinguished from chemical methods as the chemometrics.

Imaging technique is most often applied to either solid or gel samples, and has applications in chemistry, biology^{[3] [4] [5] [6] [7] [8]}, medicine^{[9] [10]}, pharmacy^[11] (see also for example: Chemical Imaging Without Dyeing ^[12]), food science, biotechnology^{[13] [14]}, agriculture and industry (see for example: NIR Chemical Imaging in Pharmaceutical Industry ^[15] and Pharmaceutical Process Analytical Technology: ^[16]). NIR, IR and Raman chemical imaging is also referred to as hyperspectral, spectroscopic, spectral or multispectral imaging (also see microspectroscopy). However, other ultra-sensitive and selective imaging techniques are also in use that involve either UV-visible or fluorescence microspectroscopy. Many imaging techniques can be used to analyze samples of all sizes, from the single molecule^{[17] [18]} to the cellular level in biology and medicine^{[19] [20] [21]}, and to images of planetary systems in astronomy, but different instrumentation is employed for making observations on such widely different systems.

Imaging instrumentation is composed of three components: a radiation source to illuminate the sample, a spectrally selective element, and usually a detector array (the camera) to collect the images. When many stacked spectral channels (wavelengths) are collected for different locations of the microspectrometer focus on a line or planar array in the focal plane, the data is called hyperspectral; fewer wavelength data sets are called multispectral. The data format is called a hypercube. The data set may be visualized as a three-dimensional block of data spanning two spatial dimensions (x and y), with a series of wavelengths (λ) making up the third (spectral) axis. The hypercube can be visually and mathematically treated as a series of spectrally resolved images (each image plane corresponding to the image at one wavelength) or a series of spatially resolved spectra.

Many materials, both manufactured and naturally occurring, derive their functionality from the spatial distribution of sample components. For example, extended release pharmaceutical formulations can be achieved by using a coating that acts as a barrier layer. The release of active ingredient is controlled by the presence of this barrier, and imperfections in the coating, such as discontinuities, may result in altered performance. In the semi-conductor industry, irregularities or contaminants in silicon wafers or printed micro-circuits can lead to failure of these components. The functionality of biological systems is also dependent upon chemical gradients – a single cell, tissue, and even whole organs function because of the very specific arrangement of components. It has been shown that even small changes in chemical composition and distribution may be an early indicator of disease.

Any material that depends on chemical gradients for functionality may be amenable to study by an analytical technique that couples spatial and chemical characterization. To efficiently and effectively design and manufacture such materials, the 'what' and the 'where' must both be measured. The demand for this type of analysis is increasing as manufactured materials become more complex. Chemical imaging techniques is critical to understanding modern manufactured products and in some cases is a non-destructive technique so that samples are preserved for further testing.

History

Commercially available laboratory-based chemical imaging systems emerged in the early 1990s (ref. 1-5). In addition to economic factors, such as the need for sophisticated electronics and extremely high-end computers, a significant barrier to commercialization of infrared imaging was that the focal plane array (FPA) needed to read IR images were not readily available as commercial items. As high-speed electronics and sophisticated computers became more commonplace, and infrared cameras became readily commercially available, laboratory chemical imaging systems were introduced.

Initially used for novel research in specialized laboratories, chemical imaging became a more commonplace analytical technique used for general R&D, quality assurance (QA) and quality control (QC) in less than a decade. The rapid acceptance of the technology in a variety of industries (pharmaceutical, polymers, semiconductors, security, forensics and agriculture) rests in the wealth of information characterizing both chemical composition and morphology. The parallel nature of chemical imaging data makes it possible to analyze multiple samples simultaneously for applications that require high throughput analysis in addition to characterizing a single sample.

Principles

Chemical imaging shares the fundamentals of vibrational spectroscopic techniques, but provides additional information by way of the simultaneous acquisition of spatially resolved spectra. It combines the advantages of digital imaging with the attributes of spectroscopic measurements. Briefly, vibrational spectroscopy measures the interaction of light with matter. Photons that interact with a sample are either absorbed or scattered; photons of specific energy are absorbed, and the pattern of absorption provides information, or a fingerprint, on the molecules that are present in the sample.

On the other hand, in terms of the observation setup, chemical imaging can be carried out in one of the following modes: (optical) absorption, emission (fluorescence), (optical) transmission or scattering (Raman). A consensus currently exists that the fluorescence (emission) and Raman scattering modes are the most sensitive and powerful, but also the most expensive.

In a transmission measurement, the radiation goes through a sample and is measured by a detector placed on the far side of the sample. The energy transferred from the incoming radiation to the molecule(s) can be calculated as the difference between the quantity of photons that were emitted by the source and the quantity that is measured by the detector. In a diffuse reflectance measurement, the same energy difference measurement is made, but the source and detector are located on the same side of the sample, and the photons that are measured have re-emerged from the illuminated side of the sample rather than passed through it. The energy may be measured at one or multiple wavelengths; when a series of measurements are made, the response curve is called a spectrum.

A key element in acquiring spectra is that the radiation must somehow be energy selected – either before or after interacting with the sample. Wavelength selection can be accomplished with a fixed filter, tunable filter, spectrograph, an interferometer, or other devices. For a fixed filter approach, it is not efficient to collect a significant number of wavelengths, and multispectral data are usually collected. Interferometer-based chemical imaging requires that entire spectral ranges be collected, and therefore results in hyperspectral data. Tunable filters have the flexibility to provide either multi- or hyperspectral data, depending on analytical requirements.

Spectra may be measured one point at a time using a single element detector (single-point mapping), as a line-image using a linear array detector (typically 16 to 28 pixels) (linear array mapping), or as a two-dimensional image using a Focal Plane Array (FPA)(typically 256 to 16,384 pixels) (FPA imaging). For single-point the sample is moved in the x and y directions point-by-point using a computer-controlled stage. With linear array mapping, the sample is moved line-by-line with a computer-controlled stage. FPA imaging data are collected with a two-dimensional FPA detector, hence capturing the full desired field-of-view at one time for each individual wavelength, without having to move the sample. FPA imaging, with its ability to collect tens of thousands of spectra simultaneously is orders of

magnitude faster than linear arrays which can typically collect 16 to 28 spectra simultaneously, which are in turn much faster than single-point mapping.

Terminology

Some words common in spectroscopy, optical microscopy and photography have been adapted or their scope modified for their use in chemical imaging. They include: resolution, field of view and magnification. There are two types of resolution in chemical imaging. The spectral resolution refers to the ability to resolve small energy differences; it applies to the spectral axis. The spatial resolution is the minimum distance between two objects that is required for them to be detected as distinct objects. The spatial resolution is influenced by the field of view, a physical measure of the size of the area probed by the analysis. In imaging, the field of view is a product of the magnification and the number of pixels in the detector array. The magnification is a ratio of the physical area of the detector array divided by the area of the sample field of view. Higher magnifications for the same detector image a smaller area of the sample.

Types of vibrational chemical imaging instruments

Chemical imaging has been implemented for mid-infrared, near-infrared spectroscopy and Raman spectroscopy. As with their bulk spectroscopy counterparts, each imaging technique has particular strengths and weaknesses, and are best suited to fulfill different needs.

Mid-infrared chemical imaging

Mid-infrared (MIR) spectroscopy probes fundamental molecular vibrations, which arise in the spectral range 2,500–25,000 nm. Commercial imaging implementations in the MIR region typically employ Fourier Transform Infrared (FT-IR) interferometers and the range is more commonly presented in wavenumber, 4,000 – 400 cm^{-1} . The MIR absorption bands tend to be relatively narrow and well-resolved; direct spectral interpretation is often possible by an experienced spectroscopist. MIR spectroscopy can distinguish subtle changes in chemistry and structure, and is often used for the identification of unknown materials. The absorptions in this spectral range are relatively strong; for this reason, sample presentation is important to limit the amount of material interacting with the incoming radiation in the MIR region. Most data collected in this range is collected in transmission mode through thin sections (~10 micrometres) of material. Water is a very strong absorber of MIR radiation and wet samples often require advanced sampling procedures (such as attenuated total reflectance). Commercial instruments include point and line mapping, and imaging. All employ an FT-IR interferometer as wavelength selective element and light source.

For types of MIR microscope, see [Microscopy#Infrared microscopy](#).

Atmospheric windows in the infrared spectrum are also employed to perform chemical imaging remotely. In these spectral regions the atmospheric gases (mainly water and CO_2) present low absorption and allow infrared viewing over kilometer distances. Target molecules can then be viewed using the selective absorption/emission processes described above.

An example of the chemical imaging of a simultaneous release of SF_6 and NH_3 is shown in the image.



Remote chemical imaging of a simultaneous release of SF_6 and NH_3 at 1.5km using the FIRST imaging spectrometer^[22]

Near-infrared chemical imaging

The analytical near infrared (NIR) region spans the range from approximately 700-2,500 nm. The absorption bands seen in this spectral range arise from overtones and combination bands of O-H, N-H, C-H and S-H stretching and bending vibrations. Absorption is one to two orders of magnitude smaller in the NIR compared to the MIR; this phenomenon eliminates the need for extensive sample preparation. Thick and thin samples can be analyzed without any sample preparation, it is possible to acquire NIR chemical images through some packaging materials, and the technique can be used to examine hydrated samples, within limits. Intact samples can be imaged in transmittance or diffuse reflectance.

The lineshapes for overtone and combination bands tend to be much broader and more overlapped than for the fundamental bands seen in the MIR. Often, multivariate methods are used to separate spectral signatures of sample components. NIR chemical imaging is particularly useful for performing rapid, reproducible and non-destructive analyses of known materials^{[23] [24]}. NIR imaging instruments are typically based on one of two platforms: imaging using a tunable filter and broad band illumination, and line mapping employing an FT-IR interferometer as the wavelength filter and light source.

Raman chemical imaging

The Raman shift chemical imaging spectral range spans from approximately 50 to 4,000 cm^{-1} ; the actual spectral range over which a particular Raman measurement is made is a function of the laser excitation frequency. The basic principle behind Raman spectroscopy differs from the MIR and NIR in that the x-axis of the Raman spectrum is measured as a function of energy shift (in cm^{-1}) relative to the frequency of the laser used as the source of radiation. Briefly, the Raman spectrum arises from inelastic scattering of incident photons, which requires a change in polarizability with vibration, as opposed to infrared absorption, which requires a change in dipole moment with vibration. The end result is spectral information that is similar and in many cases complementary to the MIR. The Raman effect is weak - only about one in 10^7 photons incident to the sample undergoes Raman scattering. Both organic and inorganic materials possess a Raman spectrum; they generally produce sharp bands that are chemically specific. Fluorescence is a competing phenomenon and, depending on the sample, can overwhelm the Raman signal, for both bulk spectroscopy and imaging implementations.

Raman chemical imaging requires little or no sample preparation. However, physical sample sectioning may be used to expose the surface of interest, with care taken to obtain a surface that is as flat as possible. The conditions required for a particular measurement dictate the level of invasiveness of the technique, and samples that are sensitive to high power laser radiation may be damaged during analysis. It is relatively insensitive to the presence of water in the sample and is therefore useful for imaging samples that contain water such as biological material.

Fluorescence imaging (visible and NIR)

This emission microspectroscopy mode is the most sensitive in both visible and FT-NIR microspectroscopy, and has therefore numerous biomedical, biotechnological and agricultural applications. There are several powerful, highly specific and sensitive fluorescence techniques that are currently in use, or still being developed; among the former are FLIM, FRAP, FRET and FLIM-FRET; among the latter are NIR fluorescence and probe-sensitivity enhanced NIR fluorescence microspectroscopy and nanospectroscopy techniques (see "Further reading" section).

Sampling and samples

The value of imaging lies in the ability to resolve spatial heterogeneities in solid-state or gel/gel-like samples. Imaging a liquid or even a suspension has limited use as constant sample motion serves to average spatial information, unless ultra-fast recording techniques are employed as in fluorescence correlation microspectroscopy or FLIM observations where a single molecule may be monitored at extremely high (photon) detection speed. High-throughput experiments (such as imaging multi-well plates) of liquid samples can however provide valuable

information. In this case, the parallel acquisition of thousands of spectra can be used to compare differences between samples, rather than the more common implementation of exploring spatial heterogeneity within a single sample.

Similarly, there is no benefit in imaging a truly homogeneous sample, as a single point spectrometer will generate the same spectral information. Of course the definition of homogeneity is dependent on the spatial resolution of the imaging system employed. For MIR imaging, where wavelengths span from 3-10 micrometres, objects on the order of 5 micrometres may theoretically be resolved. The sampled areas are limited by current experimental implementations because illumination is provided by the interferometer. Raman imaging may be able to resolve particles less than 1 micrometre in size, but the sample area that can be illuminated is severely limited. With Raman imaging, it is considered impractical to image large areas and, consequently, large samples. FT-NIR chemical/hyperspectral imaging usually resolves only larger objects (>10 micrometres), and is better suited for large samples because illumination sources are readily available. However, FT-NIR microspectroscopy was recently reported to be capable of about 1.2 micron (micrometer) resolution in biological samples^[25] Furthermore, two-photon excitation FCS experiments were reported to have attained 15 nanometer resolution on biomembrane thin films with a special coincidence photon-counting setup.

Detection limit

The concept of the detection limit for chemical imaging is quite different than for bulk spectroscopy, as it depends on the sample itself. Because a bulk spectrum represents an average of the materials present, the spectral signatures of trace components are simply overwhelmed by dilution. In imaging however, each pixel has a corresponding spectrum. If the physical size of the trace contaminant is on the order of the pixel size imaged on the sample, its spectral signature will likely be detectable. If however, the trace component is dispersed homogeneously (relative to pixel image size) throughout a sample, it will not be detectable. Therefore, detection limits of chemical imaging techniques are strongly influenced by particle size, the chemical and spatial heterogeneity of the sample, and the spatial resolution of the image.

Data analysis

Data analysis methods for chemical imaging data sets typically employ mathematical algorithms common to single point spectroscopy or to image analysis. The reasoning is that the spectrum acquired by each detector is equivalent to a single point spectrum; therefore pre-processing, chemometrics and pattern recognition techniques are utilized with the similar goal to separate chemical and physical effects and perform a qualitative or quantitative characterization of individual sample components. In the spatial dimension, each chemical image is equivalent to a digital image and standard image analysis and robust statistical analysis can be used for feature extraction.

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External links

- NIR Chemical Imaging in Pharmaceutical Industry (http://www.spectroscopyeurope.com/NIR_14_3.pdf)
- Pharmaceutical Process Analytical Technology: (<http://www.fda.gov/cder/OPS/PAT.htm>)
- NIR Chemical Imaging for Counterfeit Pharmaceutical Product Analysis (<http://www.spectroscopymag.com/spectroscopy/Near-IR+Spectroscopy/NIR-Chemical-Imaging-for-Counterfeit-Pharmaceutica/ArticleStandard/Article/detail/406629>)
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- Applications of Chemical Imaging in Research (<http://www3.imperial.ac.uk/vibrationspectroscopyandchemicalimaging/research>)

Multispectral imaging

A **Multi-spectral image** is one that captures image data at specific frequencies across the electromagnetic spectrum. The wavelengths may be separated by filters or by the use of instruments that are sensitive to particular wavelengths, including light from frequencies beyond the visible light range, such as infrared. Multi-spectral imaging can allow extraction of additional information that the human eye fails to capture with its receptors for red, green and blue. It was originally developed for space-based imaging.

Multi-spectral images are the main type of images acquired by Remote sensing (RS) radiometers. Dividing the spectrum into many bands, multi-spectral is the opposite of panchromatic which records only the total intensity of radiation falling on each pixel. Usually satellites have 3 to 7 or more radiometers (Landsat has 7). Each one acquires one digital image (in remote sensing, called a *scene*) in a small band of visible spectra, ranging 0.7 μm to 0.4 μm , called red-green-blue (RGB) region, and going to infra-red wavelengths of 0.7 μm to 10 or more μm , classified as NIR-Near InfraRed, MIR-Middle InfraRed and FIR-Far InfraRed or Thermal. In the Landsat case the 7 scenes comprise a 7 band multi spectral image. Multispectral images with more numerous bands or finer spectral resolution or wider spectral coverage may be called "hyperspectral" or "ultra-spectral".

This technology has also assisted in the interpretation of ancient papyri such as those found at Herculaneum, by imaging the fragments in the infrared range (1000nm). Often the text on the documents appears to be as black ink on black paper to the naked eye. At 1000nm, the difference in light reflectivity makes the text clearly readable. It has also been used to image the Archimedes Palimpsest by imaging the parchment leaves in bandwidths from 365-870 nm and then using advanced digital image processing techniques to reveal the under text of Archimedes work.

The availability of wavelengths for remote sensing and imaging is limited by infrared window and optical window.

Spectral bands

The wavelengths are approximate; exact values depend on the particular satellite's instruments:

- **Blue**, 450-515..520 nm, used for atmospheric and deep water imaging. Can reach within 150 feet (46 m) deep in clear water.
 - **Green**, 515..520-590..600 nm, used for imaging of vegetation and deep water structures, up to 90 feet (27 m) in clear water.
 - **Red**, 600..630-680..690 nm, used for imaging of man-made objects, water up to 30 feet (9.1 m) deep, soil, and vegetation.
 - **Near infrared**, 750-900 nm, primarily for imaging of vegetation.
 - **Mid-infrared**, 1550-1750 nm, for imaging vegetation and soil moisture content, and some forest fires.
 - **Mid-infrared**, 2080-2350 nm, for imaging soil, moisture, geological features, silicates, clays, and fires.
 - **Thermal infrared**, 10400-12500 nm, uses emitted radiation instead of reflected, for imaging of geological structures, thermal differences in water currents, fires, and for night studies.
 - **Radar** and related technologies, useful for mapping terrain and for detecting various objects.
-

Spectral band usage

For different purposes, different combinations of spectral bands can be used. They are usually represented with red, green, and blue channels. Mapping of bands to colors depends on the purpose of the image and the personal preferences of the analysts. Thermal infrared is often omitted from consideration due to poor spatial resolution, except for special purposes.

- **True-color.** Uses only red, green, and blue channels, mapped to their respective colors. A plain color photograph. Good for analyzing man-made objects. Easy to understand for beginner analysts.
- **Green-red-infrared,** where blue channel is replaced with near infrared. Vegetation, highly reflective in near IR, then shows as blue. This combination is often used for detection of vegetation and camouflage.
- **Blue-nearIR-midIR,** where blue channel uses visible blue, green uses near-infrared (so vegetation stays green), and mid-infrared is shown as red. Such images allow seeing the water depth, vegetation coverage, soil moisture content, and presence of fires, all in a single image.

Many other combinations are in use. Near infrared is often shown as red, making vegetation covered areas appear red.

Multispectral Data Analysis Software

- MicroMSI endorsed by the NGA.
- Opticks - an open source remote sensing application.

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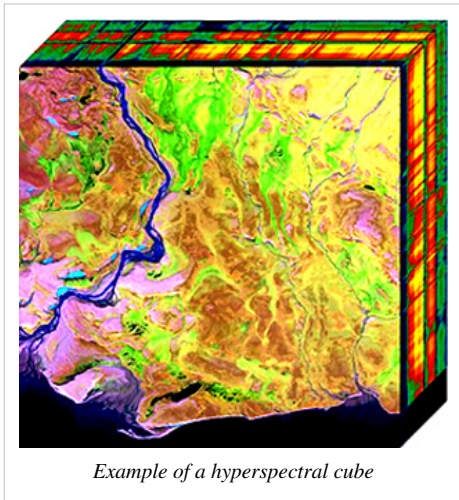
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Hyperspectral imaging

Hyperspectral imaging collects and processes information from across the electromagnetic spectrum. Unlike the human eye, which just sees visible light, hyperspectral imaging is more like the eyes of the mantis shrimp, which can see visible light as well as from the ultraviolet to infrared. Hyperspectral capabilities enable the mantis shrimp to recognize different types of coral, prey, or predators, all of which may appear as the same color to the human eye.

Humans build sensors and processing systems to provide the same type of capability for application in agriculture, mineralogy, physics, and surveillance. Hyperspectral sensors look at objects using a vast portion of the electromagnetic spectrum. Certain objects leave unique 'fingerprints' across the electromagnetic spectrum. These 'fingerprints' are known as spectral signatures and enable identification of the materials that make up a scanned object. For example, having the spectral signature for oil helps mineralogists find new oil fields.

Acquisition and Analysis



Example of a hyperspectral cube

Hyperspectral sensors collect information as a set of 'images'. Each image represents a range of the electromagnetic spectrum and is also known as a spectral band. These 'images' are then combined and form a three dimensional hyperspectral cube for processing and analysis.

Hyperspectral cubes are generated from airborne sensors like the NASA's *Airborne Visible/Infrared Imaging Spectrometer* (AVIRIS), or from satellites like NASA's Hyperion.^[1] However, for many development and validation studies handheld sensors are used.^[2]

The precision of these sensors is typically measured in spectral resolution, which is the width of each band of the spectrum that is captured. If the scanner picks up on a large number of fairly narrow frequency bands, it is possible to identify objects even if said objects are only captured in a handful of pixels. However, spatial resolution is

a factor in addition to spectral resolution. If the pixels are too large, then multiple objects are captured in the same pixel and become difficult to identify. If the pixels are too small, then the energy captured by each sensor-cell is low, and the decreased signal-to-noise ratio reduces the reliability of measured features.

MicroMSI, Opticks and Envi are three remote sensing applications that support the processing and analysis of hyperspectral data. The acquisition and processing of hyperspectral images is also referred to as imaging spectroscopy.

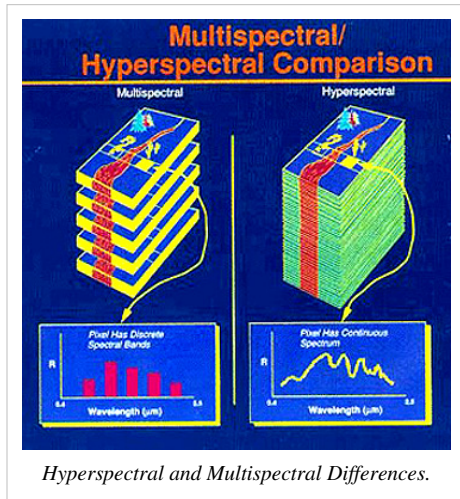
Differences between hyperspectral and multispectral imaging

Hyperspectral imaging is part of a class of techniques commonly referred to as spectral imaging or spectral analysis. Hyperspectral imaging is related to multispectral imaging. The distinction between hyper- and multi-spectral should not be based on a random or arbitrary "number of bands". A distinction that is based on the type of measurement may be more appropriate.

Multispectral deals with several images at discrete and somewhat narrow bands. The "discrete and somewhat narrow" is what distinguishes multispectral in the visible from color photography. A multispectral sensor may have many bands covering the spectrum from the visible to the longwave infrared. Multispectral images do not produce the "spectrum" of an object. Landsat is an excellent example.

Hyperspectral deals with imaging narrow spectral bands over a contiguous spectral range, and produce the spectra of all pixels in the scene. So a sensor with only 20 bands can also be hyperspectral when it covers the range from 500 to 700 nm with 20 10-nm wide bands. (While a sensor with 20 discrete bands covering the VIS, NIR, SWIR, MWIR, and LWIR would be considered multispectral.)

Ultraspectral could be reserved for interferometer type imaging sensors with a very fine spectral resolution. These sensor often have (but not necessarily) a low spatial resolution of several pixels only, a restriction imposed by the high data rate.



Hyperspectral and Multispectral Differences.

Applications

Hyperspectral remote sensing is used in a wide array of real-life applications. Although originally developed for mining and geology (the ability of hyperspectral imaging to identify various minerals makes it ideal for the mining and oil industries, where it can be used to look for ore and oil^{[2] [3]}) it has now spread into fields as widespread as ecology and surveillance, as well as historical manuscript research such as the imaging of the Archimedes Palimpsest. This technology is continually becoming more available to the public, and has been used in a wide variety of ways. Organizations such as NASA and the USGS have catalogues of various minerals and their spectral signatures, and have posted them online to make them readily available for researchers.

Agriculture

Although the costs of acquiring hyperspectral images is typically high, for specific crops and in specific climates hyperspectral remote sensing is used more and more for monitoring the development and health of crops. In Australia work is under way to use imaging spectrometers to detect grape variety, and develop an early warning system for disease outbreaks.^[4] Furthermore work is underway to use hyperspectral data to detect the chemical composition of plants^[5] which can be used to detect the nutrient and water status of wheat in irrigated systems^[6].

Another important area in agriculture is the detection of animal proteins in compound feeds in order to avoid the Bovine spongiform encephalopathy (BSE) or mad-cow disease (MCD). For this, different studies have been done in order to propose alternative tools to the reference method (classical microscopy). One of the first alternatives is the use of NIR microscopy (Infrared microscopy), which combines the advantages of microscopy and NIR. In 2004, the first study relating this problematic with Hyperspectral imaging was published^[7]. Hyperspectral libraries are constructed, which are representative of the wide diversity of ingredients usually present in the preparation of compound feeds. These libraries can be used together with chemometric tools to investigate the limit of detection, specificity and reproducibility of the NIR hyperspectral imaging method for the detection and quantification of animal ingredient in feed.

Mineralogy

The original field of development for hyperspectral remote sensing, hyperspectral sensing of minerals is now well developed. Many minerals can be identified from images, and their relation to the presence of valuable minerals such as gold and diamonds is well understood. Currently the move is towards understanding the relation between oil and gas leakages from pipelines and natural wells; their effect on the vegetation and the spectral signatures. Recent work includes the PhD dissertations of Werff^[8] and Noomen^[9].

Physics

Physicists use an electron microscopy technique that involves microanalysis using either Energy dispersive X-ray spectroscopy (EDS), Electron energy loss spectroscopy (EELS), Infrared Spectroscopy (IR), Raman Spectroscopy, or cathodoluminescence (CL) spectroscopy, in which the entire spectrum measured at each point is recorded. EELS hyperspectral imaging is performed in a scanning transmission electron microscope (STEM); EDS and CL mapping can be performed in STEM as well, or in a scanning electron microscope or electron probe microanalyzer (EPMA). Often, multiple techniques (EDS, EELS, CL) are used simultaneously.

In a "normal" mapping experiment, an image of the sample will be made that is simply the intensity of a particular emission mapped in an XY raster. For example, an EDS map could be made of a steel sample, in which iron x-ray intensity is used for the intensity grayscale of the image. Dark areas in the image would indicate not-iron-bearing impurities. This could potentially give misleading results; if the steel contained tungsten inclusions, for example, the high atomic number of tungsten could result in bremsstrahlung radiation that made the iron-free areas *appear* to be rich in iron.

By hyperspectral mapping, instead, the entire spectrum at each mapping point is acquired, and a quantitative analysis can be performed by computer post-processing of the data, and a quantitative map of iron content produced. This would show which areas contained no iron, despite the anomalous x-ray counts caused by bremsstrahlung. Because EELS core-loss edges are small signals on top of a large background, hyperspectral imaging allows large improvements to the quality of EELS chemical maps.

Similarly, in CL mapping, small shifts in the peak emission energy could be mapped, which would give information regarding slight chemical composition changes or changes in the stress state of a sample.

Surveillance

Hyperspectral surveillance is the implementation of hyperspectral scanning technology for surveillance purposes. Hyperspectral imaging is particularly useful in military surveillance because of measures that military entities now take to avoid airborne surveillance. Airborne surveillance has been in effect since soldiers used tethered balloons to spy on troops during the American Civil War, and since that time we have learned not only to hide from the naked eye, but to mask our heat signature to blend in to the surroundings and avoid infrared scanning, as well. The idea that drives hyperspectral surveillance is that hyperspectral scanning draws information from such a large portion of the light spectrum that any given object should have a unique spectral signature in at least a few of the many bands that get scanned.^[1]

Advantages and disadvantages

The primary advantages to hyperspectral imaging is that, because an entire spectrum is acquired at each point, the operator needs no prior knowledge of the sample, and post-processing allows all available information from the dataset to be mined.

The primary disadvantages are cost and complexity. Fast computers, sensitive detectors, and large data storage capacities are needed for analyzing hyperspectral data. Significant data storage capacity is necessary since hyperspectral cubes are large multi-dimensional datasets, potentially exceeding hundreds of megabytes. All of these factors greatly increase the cost of acquiring and processing hyperspectral data. Also, one of the hurdles that researchers have had to face is finding ways to program hyperspectral satellites to sort through data on their own and transmit only the most important images, as both transmission and storage of that much data could prove difficult and costly.^[1] As a relatively new analytical technique, the full potential of hyperspectral imaging has not yet been realized.

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External links

- A Matlab Hyperspectral Toolbox (<http://matlabhyperspec.sourceforge.net/>)

Spectroscopic Applications

Applied spectroscopy

Applied spectroscopy is the application of various spectroscopic methods for detection and identification of different elements/compounds in solving problems in the fields of forensics, medicine, oil industry, atmospheric chemistry, pharmacology, etc.

Spectroscopic methods

Among the more common spectroscopic methods used for analysis is FTIR spectroscopy, where chemical bonds can be detected through their characteristic infra-red absorption frequencies or wavelengths. UV spectroscopy is used where strong absorption of ultra-violet radiation occurs in a substance. Such groups are known as chromophores and include aromatic groups, conjugated system of bonds, carbonyl groups and so on. NMR spectroscopy detects hydrogen atoms in specific environments, and complements both IR and UV spectroscopy. The use of Raman spectroscopy is growing for more specialist applications.

There are also derivative methods such as infrared microscopy, which allows very small areas to be analysed in an optical microscope.

One method of elemental analysis that is important in forensic analysis is EDX performed in the environmental scanning electron microscope, or ESEM. The method involves analysis of back-scattered X-rays from the sample as a result of interaction with the electron beam.

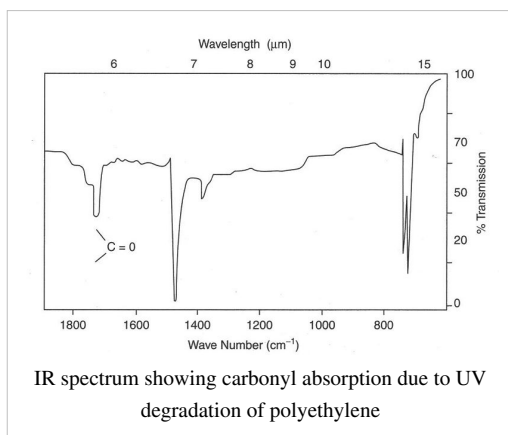
Sample preparation

In all three spectroscopic methods, the sample usually needs to be present in solution, which may present problems during forensic examination because it necessarily involves sampling solid from the object to be examined.

FTIR: Three types of samples can be analyzed, a solution (KBr), a powder, or a film. A solid film is the easiest and most straight forward sample type to test.

Analysis of polymers

Many polymer degradation mechanisms can be followed using infra-red spectroscopy, such as UV degradation and oxidation, among many other failure modes.



UV degradation

Many polymers are attacked by UV radiation at vulnerable points in their chain structures. Thus, polypropylene suffers severe cracking in sunlight unless anti-oxidants are added. The point of attack occurs at the tertiary carbon atom present in every repeat unit, causing oxidation and finally chain breakage. Polyethylene is also susceptible to UV degradation, especially those variants that are branched polymers such as LDPE. The branch points are tertiary carbon atoms, so polymer degradation starts there and results in chain cleavage, and embrittlement. In the example shown at left, carbonyl groups were readily detected by IR

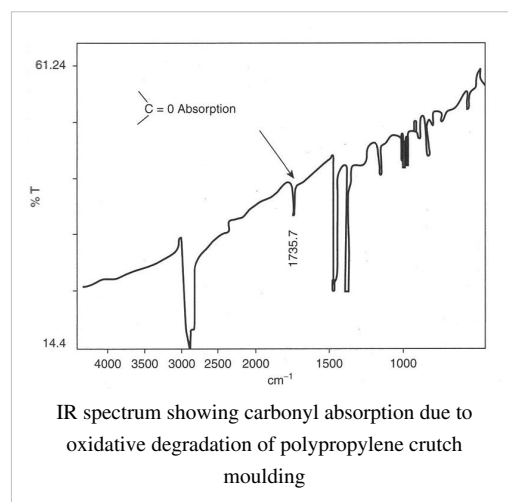
spectroscopy from a cast thin film. The product was a road cone that had cracked in service, and many similar cones also failed because an anti-UV additive had not been used.

Oxidation

Polymers are susceptible to attack by atmospheric oxygen, especially at elevated temperatures encountered during processing to shape. Many process methods such as extrusion and injection moulding involve pumping molten polymer into tools, and the high temperatures needed for melting may result in oxidation unless precautions are taken. For example, a forearm crutch suddenly snapped and the user was severely injured in the resulting fall. The crutch had fractured across a polypropylene insert within the aluminium tube of the device, and infra-red spectroscopy of the material showed that it had oxidised, possible as a result of poor moulding.

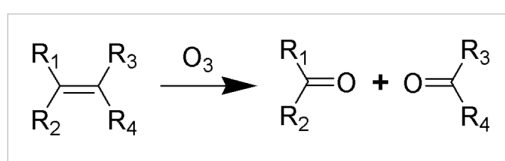
Oxidation is usually relatively easy to detect, owing to the strong absorption by the carbonyl group in the spectrum of polyolefins.

Polypropylene has a relatively simple spectrum, with few peaks at the carbonyl position (like polyethylene). Oxidation tends to start at tertiary carbon atoms because free radicals here are more stable, so last longer and are attacked by oxygen. The carbonyl group can be further oxidised to break the chain, so weakening the material by lowering the molecular weight, and cracks start to grow in the regions affected.



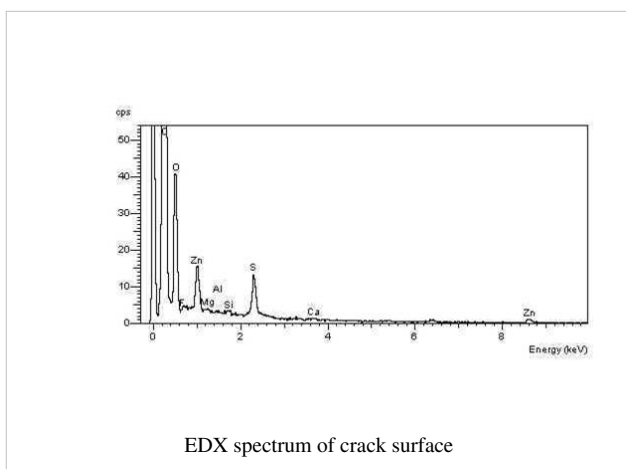
Ozonolysis

The reaction occurring between double bonds and ozone is known as ozonolysis when one molecule of the gas reacts with the double bond:

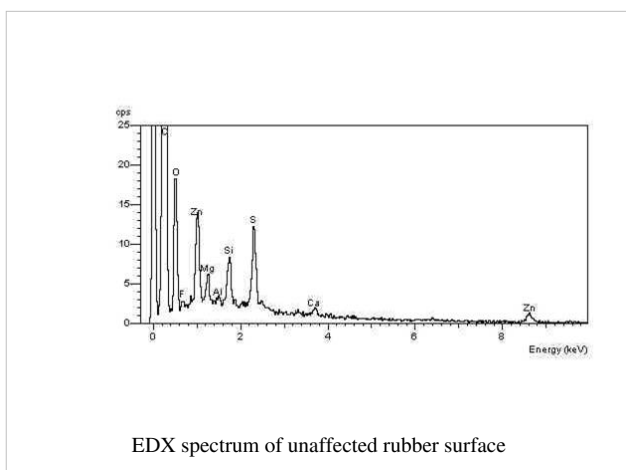


The immediate result is formation of an ozonide, which then decomposes rapidly so that the double bond is cleaved. This is the critical step in chain breakage when polymers are attacked. The strength of polymers depends on the chain molecular weight or degree of polymerization: The higher the chain length the greater the mechanical strength

(such as tensile strength). By cleaving the chain, the molecular weight drops rapidly and there comes a point when it has little strength whatsoever, and a crack forms. Further attack occurs in the freshly exposed crack surfaces and the crack grows steadily until it completes a circuit and the product separates or fails. In the case of a seal or a tube, failure occurs when the wall of the device is penetrated.



The carbonyl end groups that are formed are usually aldehydes or ketones, which can oxidise further to carboxylic acids. The net result is a high concentration of elemental oxygen on the crack surfaces, which can be detected using Energy-dispersive X-ray spectroscopy in the environmental SEM, or ESEM. The spectrum at left shows the high-oxygen peak compared with a constant sulphur peak. The spectrum at right shows the unaffected elastomer surface spectrum, with a relatively low-oxygen peak compared with the sulphur peak. The spectra were obtained during an investigation into ozone cracking of diaphragm seals in a semi-conductor fabrication factory.



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External links

- Museum of failed products ^[1]
- New Forensic course ^[2]
- The journal Engineering Failure Analysis ^[3]
- Forensic science and engineering ^[4]

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Nanotechnology

Part of a series of articles on
History Implications Applications Regulation Organizations Popular culture List of topics
Nanomaterials
Fullerene Carbon Nanotubes Nanoparticles
Nanomedicine
Nanotoxicology Nanosensor
Molecular self-assembly
Self-assembled monolayer Supramolecular assembly DNA nanotechnology
Nanoelectronics
Molecular electronics Nanolithography
Scanning probe microscopy
Atomic force microscope Scanning tunneling microscope
Molecular nanotechnology
Molecular assembler Nanorobotics Mechanosynthesis
Nanotechnology Portal

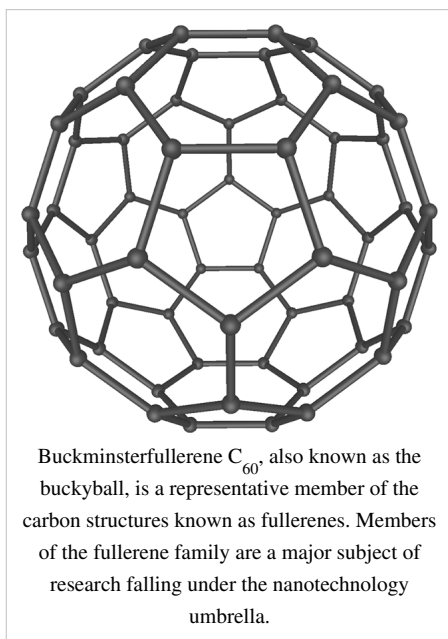
Nanotechnology (sometimes shortened to "**nanotech**") is the study of manipulating matter on an atomic and molecular scale. Generally nanotechnology deals with structures sized between 1 to 100 nanometer in at least one dimension, and involves developing materials or devices within that size. Quantum mechanical effects are very important at this scale.

Nanotechnology is very diverse, ranging from extensions of conventional device physics to completely new approaches based upon molecular self-assembly, from developing new materials with dimensions on the nanoscale to investigating whether we can directly control matter on the atomic scale.

There is much debate on the future implications of nanotechnology. Nanotechnology may be able to create many new materials and devices with a vast range of applications, such as in medicine, electronics, biomaterials and energy production. On the other hand, nanotechnology raises many of the same issues as any new technology, including concerns about the toxicity and environmental impact of nanomaterials,^[1] and their potential effects on

global economics, as well as speculation about various doomsday scenarios. These concerns have led to a debate among advocacy groups and governments on whether special regulation of nanotechnology is warranted.

Origins



The first use of the concepts found in 'nano-technology' (but pre-dating use of that name) was in "There's Plenty of Room at the Bottom", a talk given by physicist Richard Feynman at an American Physical Society meeting at Caltech on December 29, 1959. Feynman described a process by which the ability to manipulate individual atoms and molecules might be developed, using one set of precise tools to build and operate another proportionally smaller set, and so on down to the needed scale. In the course of this, he noted, scaling issues would arise from the changing magnitude of various physical phenomena: gravity would become less important, surface tension and van der Waals attraction would become increasingly more significant, etc. This basic idea appeared plausible, and exponential assembly enhances it with parallelism to produce a useful quantity of end products. The term "nanotechnology" was defined by Tokyo Science University Professor Norio Taniguchi in a 1974 paper^[2] as follows: "'Nano-technology' mainly consists of the processing of, separation, consolidation, and deformation of materials by one atom or by one molecule." In the 1980s

the basic idea of this definition was explored in much more depth by Dr. K. Eric Drexler, who promoted the technological significance of nano-scale phenomena and devices through speeches and the books *Engines of Creation: The Coming Era of Nanotechnology* (1986) and *Nanosystems: Molecular Machinery, Manufacturing, and Computation*,^[3] and so the term acquired its current sense. *Engines of Creation: The Coming Era of Nanotechnology* is considered the first book on the topic of nanotechnology. Nanotechnology and nanoscience got started in the early 1980s with two major developments; the birth of cluster science and the invention of the scanning tunneling microscope (STM). This development led to the discovery of fullerenes in 1985 and carbon nanotubes a few years later. In another development, the synthesis and properties of semiconductor nanocrystals was studied; this led to a fast increasing number of metal and metal oxide nanoparticles and quantum dots. The atomic force microscope (AFM or SFM) was invented six years after the STM was invented. In 2000, the United States National Nanotechnology Initiative was founded to coordinate Federal nanotechnology research and development and is evaluated by the President's Council of Advisors on Science and Technology.

Fundamental concepts

One nanometer (nm) is one billionth, or 10^{-9} , of a meter. By comparison, typical carbon-carbon bond lengths, or the spacing between these atoms in a molecule, are in the range 0.12–0.15 nm, and a DNA double-helix has a diameter around 2 nm. On the other hand, the smallest cellular life-forms, the bacteria of the genus *Mycoplasma*, are around 200 nm in length.

To put that scale in another context, the comparative size of a nanometer to a meter is the same as that of a marble to the size of the earth.^[4] Or another way of putting it: a nanometer is the amount an average man's beard grows in the time it takes him to raise the razor to his face.^[4]

Two main approaches are used in nanotechnology. In the "bottom-up" approach, materials and devices are built from molecular components which assemble themselves chemically by principles of molecular recognition. In the "top-down" approach, nano-objects are constructed from larger entities without atomic-level control.^[5]

Areas of physics such as nanoelectronics, nanomechanics, nanophotonics and nanoionics have evolved during the last few decades to provide a basic scientific foundation of nanotechnology.

Larger to smaller: a materials perspective

A number of physical phenomena become pronounced as the size of the system decreases. These include statistical mechanical effects, as well as quantum mechanical effects, for example the “quantum size effect” where the electronic properties of solids are altered with great reductions in particle size. This effect does not come into play by going from macro to micro dimensions. However, quantum effects become dominant when the nanometer size range is reached, typically at distances of 100 nanometers or less, the so called quantum realm. Additionally, a number of physical (mechanical, electrical, optical, etc.) properties change when compared to macroscopic systems. One example is the increase in surface area to volume ratio altering mechanical, thermal and catalytic properties of materials. Diffusion and reactions at nanoscale, nanostructures materials and nanodevices with fast ion transport are generally referred to nanoionics. *Mechanical* properties of nanosystems are of interest in the nanomechanics research. The catalytic activity of nanomaterials also opens potential risks in their interaction with biomaterials.^[6]

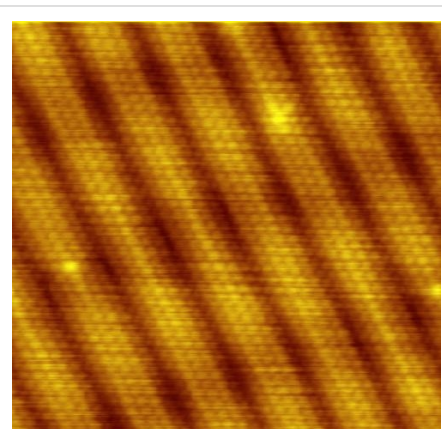


Image of reconstruction on a clean Gold(100) surface, as visualized using scanning tunneling microscopy. The positions of the individual atoms composing the surface are visible.

Materials reduced to the nanoscale can show different properties compared to what they exhibit on a macroscale, enabling unique applications. For instance, opaque substances become transparent (copper); stable materials turn combustible (aluminum); insoluble materials become soluble (gold). A material such as gold, which is chemically inert at normal scales, can serve as a potent chemical catalyst at nanoscales. Much of the fascination with nanotechnology stems from these quantum and surface phenomena that matter exhibits at the nanoscale.^[7]

Simple to complex: a molecular perspective

Modern synthetic chemistry has reached the point where it is possible to prepare small molecules to almost any structure. These methods are used today to manufacture a wide variety of useful chemicals such as pharmaceuticals or commercial polymers. This ability raises the question of extending this kind of control to the next-larger level, seeking methods to assemble these single molecules into supramolecular assemblies consisting of many molecules arranged in a well defined manner.

These approaches utilize the concepts of molecular self-assembly and/or supramolecular chemistry to automatically arrange themselves into some useful conformation through a bottom-up approach. The concept of molecular recognition is especially important: molecules can be designed so that a specific configuration or arrangement is favored due to non-covalent intermolecular forces. The Watson–Crick basepairing rules are a direct result of this, as is the specificity of an enzyme being targeted to a single substrate, or the specific folding of the protein itself. Thus, two or more components can be designed to be complementary and mutually attractive so that they make a more complex and useful whole.

Such bottom-up approaches should be capable of producing devices in parallel and be much cheaper than top-down methods, but could potentially be overwhelmed as the size and complexity of the desired assembly increases. Most useful structures require complex and thermodynamically unlikely arrangements of atoms. Nevertheless, there are many examples of self-assembly based on molecular recognition in biology, most notably Watson–Crick basepairing and enzyme–substrate interactions. The challenge for nanotechnology is whether these principles can be used to engineer new constructs in addition to natural ones.

Molecular nanotechnology: a long-term view

Molecular nanotechnology, sometimes called molecular manufacturing, describes engineered nanosystems (nanoscale machines) operating on the molecular scale. Molecular nanotechnology is especially associated with the molecular assembler, a machine that can produce a desired structure or device atom-by-atom using the principles of mechanosynthesis. Manufacturing in the context of productive nanosystems is not related to, and should be clearly distinguished from, the conventional technologies used to manufacture nanomaterials such as carbon nanotubes and nanoparticles.

When the term "nanotechnology" was independently coined and popularized by Eric Drexler (who at the time was unaware of an earlier usage by Norio Taniguchi) it referred to a future manufacturing technology based on molecular machine systems. The premise was that molecular scale biological analogies of traditional machine components demonstrated molecular machines were possible: by the countless examples found in biology, it is known that sophisticated, stochastically optimised biological machines can be produced.

It is hoped that developments in nanotechnology will make possible their construction by some other means, perhaps using biomimetic principles. However, Drexler and other researchers^[8] have proposed that advanced nanotechnology, although perhaps initially implemented by biomimetic means, ultimately could be based on mechanical engineering principles, namely, a manufacturing technology based on the mechanical functionality of these components (such as gears, bearings, motors, and structural members) that would enable programmable, positional assembly to atomic specification.^[9] The physics and engineering performance of exemplar designs were analyzed in Drexler's book *Nanosystems*.

In general it is very difficult to assemble devices on the atomic scale, as all one has to position atoms on other atoms of comparable size and stickiness. Another view, put forth by Carlo Montemagno,^[10] is that future nanosystems will be hybrids of silicon technology and biological molecular machines. Yet another view, put forward by the late Richard Smalley, is that mechanosynthesis is impossible due to the difficulties in mechanically manipulating individual molecules.

This led to an exchange of letters in the ACS publication Chemical & Engineering News in 2003.^[11] Though biology clearly demonstrates that molecular machine systems are possible, non-biological molecular machines are today only in their infancy. Leaders in research on non-biological molecular machines are Dr. Alex Zettl and his colleagues at Lawrence Berkeley Laboratories and UC Berkeley. They have constructed at least three distinct molecular devices whose motion is controlled from the desktop with changing voltage: a nanotube nanomotor, a molecular actuator,^[12] and a nanoelectromechanical relaxation oscillator.^[13]

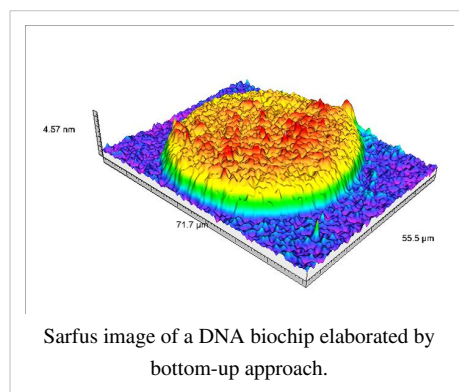
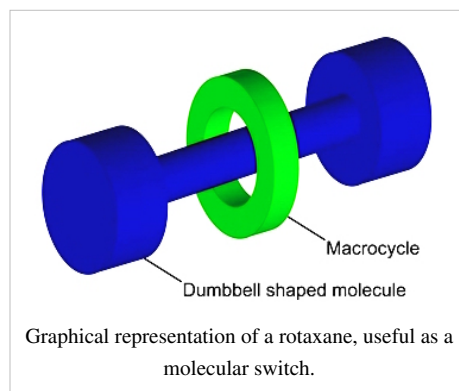
An experiment indicating that positional molecular assembly is possible was performed by Ho and Lee at Cornell University in 1999. They used a scanning tunneling microscope to move an individual carbon monoxide molecule (CO) to an individual iron atom (Fe) sitting on a flat silver crystal, and chemically bound the CO to the Fe by applying a voltage.

Current research

Nanomaterials

The nanomaterials field includes subfields which develop or study materials having unique properties arising from their nanoscale dimensions.^[15]

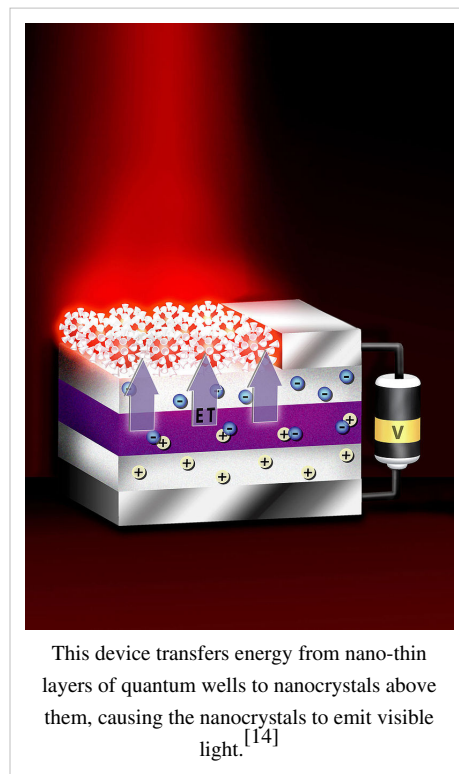
- Interface and colloid science has given rise to many materials which may be useful in nanotechnology, such as carbon nanotubes and other fullerenes, and various nanoparticles and nanorods. Nanomaterials with fast ion transport are related also to nanoionics and nanoelectronics.
- Nanoscale materials can also be used for bulk applications; most present commercial applications of nanotechnology are of this flavor.
- Progress has been made in using these materials for medical applications; see Nanomedicine.
- Nanoscale materials are sometimes used in solar cells which combats the cost of traditional Silicon solar cells
- Development of applications incorporating semiconductor nanoparticles to be used in the next generation of products, such as display technology, lighting, solar cells and biological imaging; see quantum dots.



Bottom-up approaches

These seek to arrange smaller components into more complex assemblies.

- DNA nanotechnology utilizes the specificity of Watson–Crick basepairing to construct well-defined structures out of DNA and other nucleic acids.
- Approaches from the field of "classical" chemical synthesis also aim at designing molecules with well-defined shape (e.g. bis-peptides^[16]).
- More generally, molecular self-assembly seeks to use concepts of supramolecular chemistry, and molecular recognition in particular, to cause single-molecule components to automatically arrange themselves into some useful conformation.
- Atomic force microscope tips can be used as a nanoscale "write head" to deposit a chemical upon a surface in a desired pattern in a process called dip pen nanolithography. This technique fits into the larger subfield of nanolithography.



Top-down approaches

These seek to create smaller devices by using larger ones to direct their assembly.

- Many technologies that descended from conventional solid-state silicon methods for fabricating microprocessors are now capable of creating features smaller than 100 nm, falling under the definition of nanotechnology. Giant magnetoresistance-based hard drives already on the market fit this description,^[17] as do atomic layer deposition (ALD) techniques. Peter Grünberg and Albert Fert received the Nobel Prize in Physics in 2007 for their discovery of Giant magnetoresistance and contributions to the field of spintronics.^[18]
- Solid-state techniques can also be used to create devices known as nanoelectromechanical systems or NEMS, which are related to microelectromechanical systems or MEMS.
- Focused ion beams can directly remove material, or even deposit material when suitable pre-cursor gasses are applied at the same time. For example, this technique is used routinely to create sub-100 nm sections of material for analysis in Transmission electron microscopy.
- Atomic force microscope tips can be used as a nanoscale "write head" to deposit a resist, which is then followed by an etching process to remove material in a top-down method.

Functional approaches

These seek to develop components of a desired functionality without regard to how they might be assembled.

- Molecular electronics seeks to develop molecules with useful electronic properties. These could then be used as single-molecule components in a nanoelectronic device.^[19] For an example see rotaxane.
- Synthetic chemical methods can also be used to create synthetic molecular motors, such as in a so-called nanocar.

Biomimetic approaches

- Bionics or biomimicry seeks to apply biological methods and systems found in nature, to the study and design of engineering systems and modern technology. Biomineralization is one example of the systems studied.
- Bionanotechnology the use of biomolecules for applications in nanotechnology, including use of viruses.^[20]

Speculative

These subfields seek to anticipate what inventions nanotechnology might yield, or attempt to propose an agenda along which inquiry might progress. These often take a big-picture view of nanotechnology, with more emphasis on its societal implications than the details of how such inventions could actually be created.

- Molecular nanotechnology is a proposed approach which involves manipulating single molecules in finely controlled, deterministic ways. This is more theoretical than the other subfields and is beyond current capabilities.
- Nanorobotics centers on self-sufficient machines of some functionality operating at the nanoscale. There are hopes for applying nanorobots in medicine,^{[21] [22] [23]} but it may not be easy to do such a thing because of several drawbacks of such devices.^[24] Nevertheless, progress on innovative materials and methodologies has been demonstrated with some patents granted about new nanomanufacturing devices for future commercial applications, which also progressively helps in the development towards nanorobots with the use of embedded nanobioelectronics concepts.^{[25] [26]}
- Productive nanosystems are "systems of nanosystems" which will be complex nanosystems that produce atomically precise parts for other nanosystems, not necessarily using novel nanoscale-emergent properties, but well-understood fundamentals of manufacturing. Because of the discrete (i.e. atomic) nature of matter and the possibility of exponential growth, this stage is seen as the basis of another industrial revolution. Mihail Roco, one of the architects of the USA's National Nanotechnology Initiative, has proposed four states of nanotechnology that seem to parallel the technical progress of the Industrial Revolution, progressing from passive nanostructures to active nanodevices to complex nanomachines and ultimately to productive nanosystems.^[27]
- Programmable matter seeks to design materials whose properties can be easily, reversibly and externally controlled through a fusion of information science and materials science.

- Due to the popularity and media exposure of the term nanotechnology, the words picotechnology and femtotechnology have been coined in analogy to it, although these are only used rarely and informally.

Tools and techniques

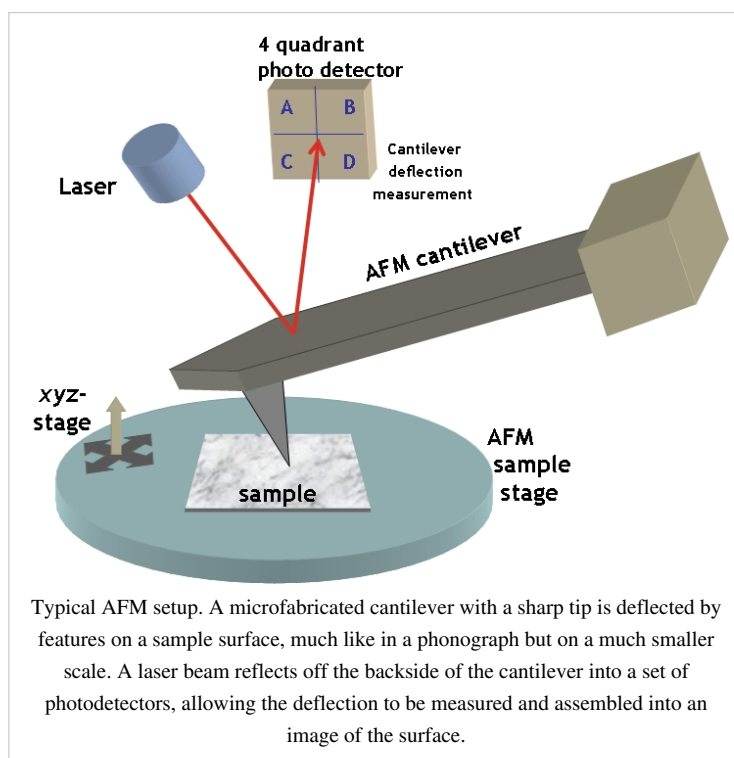
There are several important modern developments. The atomic force microscope (AFM) and the Scanning Tunneling Microscope (STM) are two early versions of scanning probes that launched nanotechnology. There are other types of scanning probe microscopy, all flowing from the ideas of the scanning confocal microscope developed by Marvin Minsky in 1961 and the scanning acoustic microscope (SAM) developed by Calvin Quate and coworkers in the 1970s, that made it possible to see structures at the nanoscale. The tip of a scanning probe can also be used to manipulate nanostructures (a process called positional assembly). Feature-oriented scanning-positioning methodology suggested by Rostislav Lapshin appears to be a promising way to implement these nanomanipulations in automatic mode.

However, this is still a slow process because of low scanning velocity of the microscope. Various techniques of nanolithography such as optical lithography, X-ray lithography dip pen nanolithography, electron beam lithography or nanoimprint lithography were also developed. Lithography is a top-down fabrication technique where a bulk material is reduced in size to nanoscale pattern.

Another group of nanotechnological techniques include those used for fabrication of nanowires, those used in semiconductor fabrication such as deep ultraviolet lithography, electron beam lithography, focused ion beam machining, nanoimprint lithography, atomic layer deposition, and molecular vapor deposition, and further including molecular self-assembly techniques such as those employing di-block copolymers. However, all of these techniques preceded the nanotech era, and are extensions in the development of scientific advancements rather than techniques which were devised with the sole purpose of creating nanotechnology and which were results of nanotechnology research.

The top-down approach anticipates nanodevices that must be built piece by piece in stages, much as manufactured items are made. Scanning probe microscopy is an important technique both for characterization and synthesis of nanomaterials. Atomic force microscopes and scanning tunneling microscopes can be used to look at surfaces and to move atoms around. By designing different tips for these microscopes, they can be used for carving out structures on surfaces and to help guide self-assembling structures. By using, for example, feature-oriented scanning-positioning approach, atoms can be moved around on a surface with scanning probe microscopy techniques. At present, it is expensive and time-consuming for mass production but very suitable for laboratory experimentation.

In contrast, bottom-up techniques build or grow larger structures atom by atom or molecule by molecule. These techniques include chemical synthesis, self-assembly and positional assembly. Dual polarisation interferometry is one tool suitable for characterisation of self assembled thin films. Another variation of the bottom-up approach is



molecular beam epitaxy or MBE. Researchers at Bell Telephone Laboratories like John R. Arthur, Alfred Y. Cho, and Art C. Gossard developed and implemented MBE as a research tool in the late 1960s and 1970s. Samples made by MBE were key to the discovery of the fractional quantum Hall effect for which the 1998 Nobel Prize in Physics was awarded. MBE allows scientists to lay down atomically precise layers of atoms and, in the process, build up complex structures. Important for research on semiconductors, MBE is also widely used to make samples and devices for the newly emerging field of spintronics.

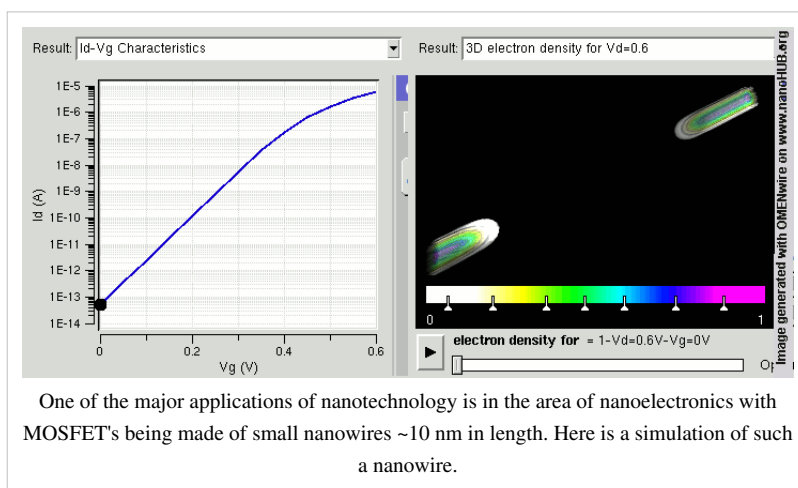
However, new therapeutic products, based on responsive nanomaterials, such as the ultradeformable, stress-sensitive Transfersome vesicles, are under development and already approved for human use in some countries.

Applications

As of August 21, 2008, the Project on Emerging Nanotechnologies estimates that over 800 manufacturer-identified nanotech products are publicly available, with new ones hitting the market at a pace of 3–4 per week.^[28] The project lists all of the products in a publicly accessible online.^[29] Most applications are limited to the use of "first generation" passive nanomaterials which includes titanium dioxide in sunscreen, cosmetics and some food products; Carbon allotropes used to produce gecko tape; silver in food packaging, clothing, disinfectants and household appliances; zinc oxide in sunscreens and cosmetics, surface coatings, paints and outdoor furniture varnishes; and cerium oxide as a fuel catalyst.^[30]

The National Science Foundation (a major distributor for nanotechnology research in the United States) funded researcher David Berube to study the field of nanotechnology. His findings are published in the monograph *Nano-Hype: The Truth Behind the Nanotechnology Buzz*.^[31] This study concludes that much of what is sold as "nanotechnology" is in fact a recasting of straightforward materials science, which is leading to a "nanotech industry built solely on selling

nanotubes, nanowires, and the like" which will "end up with a few suppliers selling low margin products in huge volumes." Further applications which require actual manipulation or arrangement of nanoscale components await further research. Though technologies branded with the term 'nano' are sometimes little related to and fall far short of the most ambitious and transformative technological goals of the sort in molecular manufacturing proposals, the term still connotes such ideas. According to Berube, there may be a danger that a "nano bubble" will form, or is forming already, from the use of the term by scientists and entrepreneurs to garner funding, regardless of interest in the transformative possibilities of more ambitious and far-sighted work.^[32]



Implications

Because of the far-ranging claims that have been made about potential applications of nanotechnology, a number of serious concerns have been raised about what effects these will have on our society if realized, and what action if any is appropriate to mitigate these risks.

There are possible dangers that arise with the development of nanotechnology. The Center for Responsible Nanotechnology suggests that new developments could result, among other things, in untraceable weapons of mass destruction, networked cameras for use by the government, and weapons developments fast enough to destabilize arms races ("Nanotechnology Basics").

One area of concern is the effect that industrial-scale manufacturing and use of nanomaterials would have on human health and the environment, as suggested by nanotoxicology research. Groups such as the Center for Responsible Nanotechnology have advocated that nanotechnology should be specially regulated by governments for these reasons. Others counter that overregulation would stifle scientific research and the development of innovations which could greatly benefit mankind.

Other experts, including director of the Woodrow Wilson Center's Project on Emerging Nanotechnologies David Rejeski, have testified^[33] that successful commercialization depends on adequate oversight, risk research strategy, and public engagement. Berkeley, California is currently the only city in the United States to regulate nanotechnology,^[34] Cambridge, Massachusetts in 2008 considered enacting a similar law,^[35] but ultimately rejected this.^[36]

Health and environmental concerns

Some of the recently developed nanoparticle products may have unintended consequences. Researchers have discovered that silver nanoparticles used in socks only to reduce foot odor are being released in the wash with possible negative consequences.^[37] Silver nanoparticles, which are bacteriostatic, may then destroy beneficial bacteria which are important for breaking down organic matter in waste treatment plants or farms.^[38]

A study at the University of Rochester found that when rats breathed in nanoparticles, the particles settled in the brain and lungs, which led to significant increases in biomarkers for inflammation and stress response.^[39] A study in China indicated that nanoparticles induce skin aging through oxidative stress in hairless mice.^{[40] [41]}

A two-year study at UCLA's School of Public Health found lab mice consuming nano-titanium dioxide showed DNA and chromosome damage to a degree "linked to all the big killers of man, namely cancer, heart disease, neurological disease and aging".^[42]

A major study published more recently in *Nature Nanotechnology* suggests some forms of carbon nanotubes – a poster child for the “nanotechnology revolution” – could be as harmful as asbestos if inhaled in sufficient quantities. Anthony Seaton of the Institute of Occupational Medicine in Edinburgh, Scotland, who contributed to the article on carbon nanotubes said "We know that some of them probably have the potential to cause mesothelioma. So those sorts of materials need to be handled very carefully."^[43] In the absence of specific nano-regulation forthcoming from governments, Paull and Lyons (2008) have called for an exclusion of engineered nanoparticles from organic food.^[44] A newspaper article reports that workers in a paint factory developed serious lung disease and nanoparticles were found in their lungs.^[45]

Regulation

Calls for tighter regulation of nanotechnology have occurred alongside a growing debate related to the human health and safety risks associated with nanotechnology.^[46] Furthermore, there is significant debate about who is responsible for the regulation of nanotechnology. While some non-nanotechnology specific regulatory agencies currently cover some products and processes (to varying degrees) – by “bolting on” nanotechnology to existing regulations – there are clear gaps in these regimes.^[47] In "Nanotechnology Oversight: An Agenda for the Next Administration,"^[48]

former EPA deputy administrator J. Clarence (Terry) Davies lays out a clear regulatory roadmap for the next presidential administration and describes the immediate and longer term steps necessary to deal with the current shortcomings of nanotechnology oversight.

Stakeholders concerned by the lack of a regulatory framework to assess and control risks associated with the release of nanoparticles and nanotubes have drawn parallels with bovine spongiform encephalopathy ('mad cow's disease'), thalidomide, genetically modified food,^[49] nuclear energy, reproductive technologies, biotechnology, and asbestosis. Dr. Andrew Maynard, chief science advisor to the Woodrow Wilson Center's Project on Emerging Nanotechnologies, concludes (among others) that there is insufficient funding for human health and safety research, and as a result there is currently limited understanding of the human health and safety risks associated with nanotechnology.^[50] As a result, some academics have called for stricter application of the precautionary principle, with delayed marketing approval, enhanced labelling and additional safety data development requirements in relation to certain forms of nanotechnology.^[51]

The Royal Society report^[52] identified a risk of nanoparticles or nanotubes being released during disposal, destruction and recycling, and recommended that "manufacturers of products that fall under extended producer responsibility regimes such as end-of-life regulations publish procedures outlining how these materials will be managed to minimize possible human and environmental exposure" (p.xiii). Reflecting the challenges for ensuring responsible life cycle regulation, the Institute for Food and Agricultural Standards^[53] has proposed standards for nanotechnology research and development should be integrated across consumer, worker and environmental standards. They also propose that NGOs and other citizen groups play a meaningful role in the development of these standards.

In October 2008, the Department of Toxic Substances Control (DTSC), within the California Environmental Protection Agency, announced its intent to request information regarding analytical test methods, fate and transport in the environment, and other relevant information from manufacturers of carbon nanotubes.^[54] The purpose of this information request will be to identify information gaps and to develop information about carbon nanotubes, an important emerging nanomaterial.

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External links

- What is Nanotechnology? (<http://www.vega.org.uk/video/programme/3>) (A Vega/BBC/OU Video Discussion).
 - Nanotec Expo (<http://www.nanotecexpo.com.br/english>) - Fair and Congress Latin American of Nanotechnology
 - "Nanotechnology Basics: For Students and Other Learners." (<http://www.crnano.org/basics.htm>) Center for Responsible Nanotechnology. World Care. 11 Nov. 2008.
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Nuclear medicine

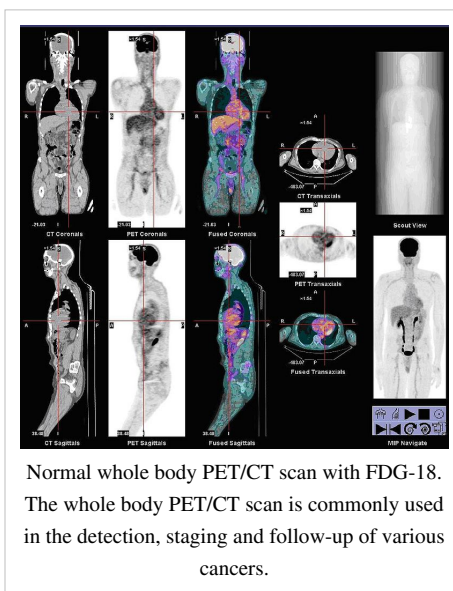
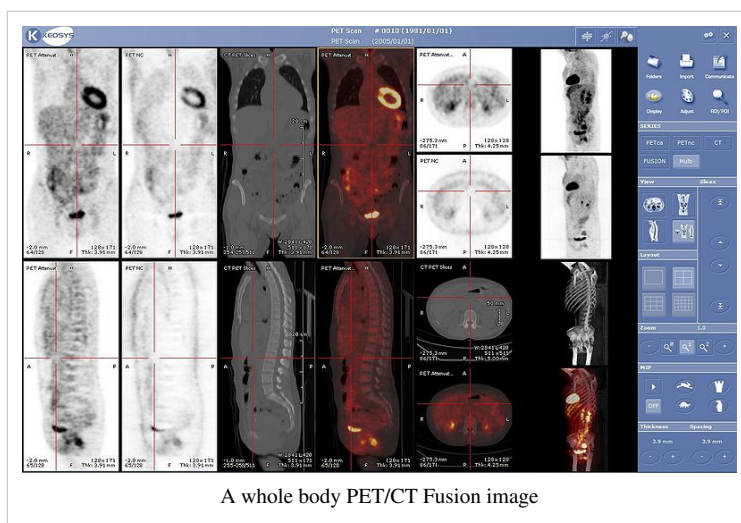
Nuclear medicine is a branch or specialty of medicine and medical imaging that uses radionuclides and relies on the process of radioactive decay in the diagnosis and treatment of disease.

In nuclear medicine procedures, elemental radionuclides are combined with other elements to form chemical compounds, or else combined with existing pharmaceutical compounds, to form radiopharmaceuticals. These radiopharmaceuticals, once administered to the patient, can localize to specific organs or cellular receptors. This property of radiopharmaceuticals allows nuclear medicine the ability to **image** the extent of a disease-process in the body, based on the cellular function and physiology, rather than relying on physical changes in the tissue anatomy. In some diseases nuclear medicine studies can identify medical problems at an earlier stage than other diagnostic tests.

Treatment of diseased tissue, based on metabolism or uptake or binding of a particular ligand, may also be accomplished, similar to other areas of pharmacology. However, the treatment effects of radiopharmaceuticals rely on the tissue-destructive power of short-range ionizing radiation.

Description of the field

In nuclear medicine imaging, radiopharmaceuticals are taken internally, for example intravenously or orally. Then, external detectors (gamma cameras) capture and form images from the radiation emitted by the radiopharmaceuticals. This process is unlike a diagnostic X-ray where external radiation is passed through the body to form an image.



There are several techniques of diagnostic nuclear medicine. *Scintigraphy* ("scint") is the use of internal radionuclides to create two-dimensional^[1] images. *SPECT* is a 3D tomographic technique that uses gamma camera data from many projections and can be reconstructed in different planes. *Positron emission tomography* (PET) uses coincidence detection to image functional processes.

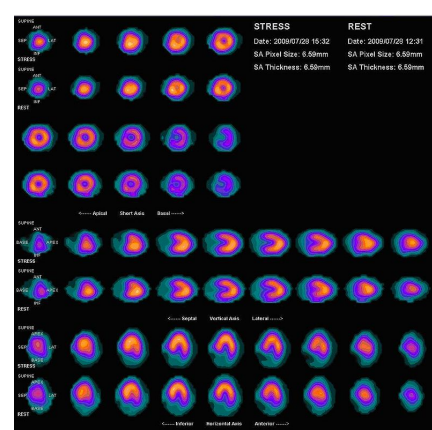
Nuclear medicine tests differ from most other imaging modalities in that diagnostic tests primarily show the physiological function of the system being investigated as opposed to traditional anatomical imaging such as CT or MRI. Nuclear medicine imaging studies are generally more organ or tissue specific (e.g.: lungs scan, heart scan, bone scan, brain scan, etc.) than those in conventional radiology imaging, which focus on a particular section of the body (e.g.: chest X-ray, abdomen/pelvis CT scan, head CT scan, etc.). In addition, there are nuclear medicine studies that allow imaging of the whole body based on certain cellular receptors or functions. Examples are whole body PET scan or PET/CT scans, gallium scans, indium white blood cell scans, MIBG and octreotide scans.

While the ability of nuclear metabolism to image disease processes from differences in metabolism is unsurpassed, it is not unique. Certain techniques such as fMRI image tissues (particularly cerebral tissues) by blood flow, and thus show metabolism. Also, contrast-enhancement techniques in both CT and MRI show regions of tissue which are handling pharmaceuticals differently, due to an inflammatory process.

Diagnostic tests in nuclear medicine exploit the way that the body handles substances differently when there is disease or pathology present. The radionuclide introduced into the body is often chemically bound to a complex that acts characteristically within the body; this is commonly known as a tracer. In the presence of disease, a tracer will often be distributed around the body and/or processed differently. For example, the ligand methylene-diphosphonate (MDP) can be preferentially taken up by bone. By chemically attaching technetium-99m to MDP, radioactivity can be transported and attached to bone via the hydroxyapatite for imaging. Any increased physiological function, such as due to a fracture in the bone, will usually mean increased concentration of the tracer. This often results in the appearance of a 'hot-spot' which is a focal increase in radio-accumulation, or a general increase in radio-accumulation throughout the physiological system. Some disease processes result in the exclusion of a tracer, resulting in the appearance of a 'cold-spot'. Many tracer complexes have been developed to image or treat many different organs, glands, and physiological processes.



A nuclear medicine whole body bone scan. The nuclear medicine whole body bone scan is generally used in evaluations of various bone related pathology, such as for bone pain, stress fracture, nonmalignant bone lesions, bone infections, or the spread of cancer to the bone.



Nuclear Medicine myocardial perfusion scan with Thallium-201 for the rest images (bottom rows) and Tc-Sestamibi for the stress images (top rows). The nuclear medicine myocardial perfusion scan plays a pivotal role in the noninvasive evaluation of coronary artery disease. The study not only identifies patients with coronary artery disease, it also provides overall prognostic information or overall risk of adverse cardiac events for the patient.

Hybrid scanning techniques

In some centers, the nuclear medicine scans can be superimposed, using software or hybrid cameras, on images from modalities such as CT or MRI to highlight the part of the body in which the radiopharmaceutical is concentrated. This practice is often referred to as image fusion or co-registration, for example SPECT/CT and PET/CT. The fusion imaging technique in nuclear medicine provides information about the anatomy and function, which would otherwise be unavailable, or would require a more invasive procedure or surgery.

Practical concerns in nuclear imaging

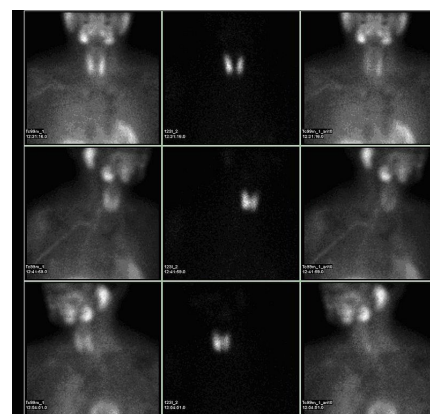
The amount of radiation from diagnostic nuclear medicine procedures is kept within a safe limit and follows the "ALARA" (As Low As Reasonably Achievable) principle. The radiation dose from nuclear medicine imaging varies greatly depending on the type of study. The effective radiation dose can be lower than or comparable to the annual background radiation dose. It can also be in the range or higher than the radiation dose from an abdomen/pelvis CT scan.[2]

Some nuclear medicine procedures require special patient preparation before the study to obtain the most accurate result. Pre-imaging preparations may include dietary preparation or the withholding of certain medications. Patients are encouraged to consult with the nuclear medicine department prior to a scan.

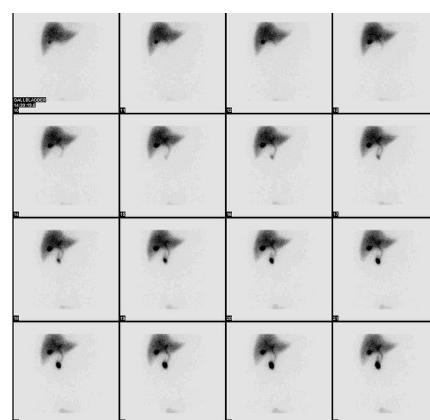
Nuclear medicine therapy

In nuclear medicine therapy, the radiation treatment dose is administered internally (e.g. intravenous or oral routes) rather than from an external radiation source.

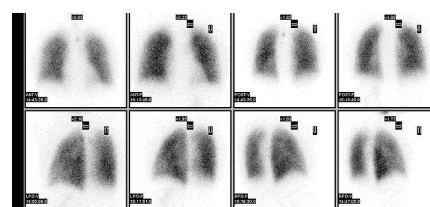
The radiopharmaceuticals used in Nuclear Medicine therapy emit ionizing radiation that travels only a short distance, thereby minimizing unwanted side effects and damage to noninvolved organs or nearby structures. Most Nuclear Medicine therapies can be performed as outpatient procedures since there are few side effects from the treatment and the radiation exposure to the general public can be kept within a safe limit. Common Nuclear Medicine therapies include ^{131}I -sodium iodide for hyperthyroidism and thyroid cancer, Yttrium-90-ibritumomab tiuxetan (Zevalin) and Iodine-131-tositumomab (Bexxar) for refractory Lymphoma, ^{131}I -MIBG (metaiodobenzylguanidine) for neuroendocrine tumors, and palliative bone pain treatment with Samarium-153 or Strontium-89. In some centers the nuclear medicine department may also use implanted capsules of isotopes (brachytherapy) to treat cancer.



A nuclear medicine parathyroid scan demonstrates a parathyroid adenoma adjacent to the left inferior pole of the thyroid gland. The above study was performed with Technetium-Sestamibi (1st column) and Iodine-123 (2nd column) simultaneous imaging and the subtraction technique (3rd column).



Normal hepatobiliary scan (HIDA scan). The nuclear medicine hepatobiliary scan is clinically useful in the detection of the gallbladder disease.

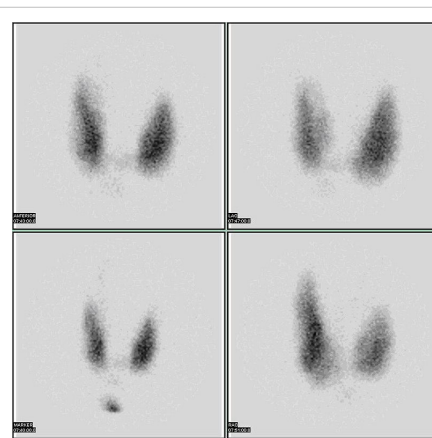


Normal pulmonary ventilation and perfusion (V/Q) scan. The nuclear medicine V/Q scan is useful in the evaluation of pulmonary embolism.

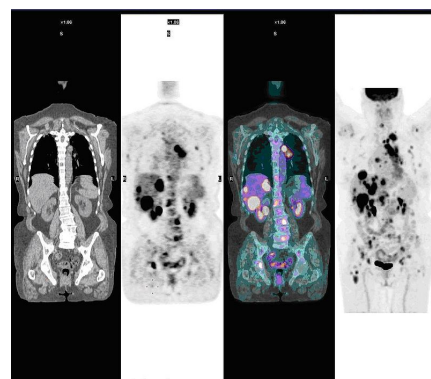
Most nuclear medicine therapies will also require appropriate patient preparation prior to a treatment. Therefore, consultation with the Nuclear Medicine department is recommended prior to therapy.

Molecular medicine

In the future, nuclear medicine may be known as molecular medicine. As our understanding of biological processes in the cells of living organism expands, specific probes can be developed to allow visualization, characterization, and quantification of biologic processes at the cellular and subcellular levels.^[2] Nuclear Medicine is an ideal specialty to adapt to the new discipline of molecular medicine, because of its emphasis on function and its utilization of imaging agents that are specific for a particular disease process.



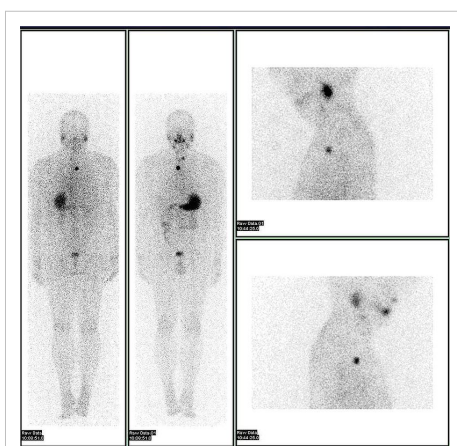
Thyroid scan with Iodine-123 for evaluation of hyperthyroidism.



Abnormal whole body PET/CT scan with multiple metastases from a cancer. The whole body PET/CT scan has become an important tool in the evaluation of cancer.



A nuclear medicine SPECT liver scan with technetium-99m labeled autologous red blood cells. A focus of high uptake (arrow) in the liver is consistent with a hemangioma.



Iodine-123 whole body scan for thyroid cancer evaluation. The study above was performed after the total thyroidectomy and TSH stimulation with thyroid hormone medication withdrawal. The study shows a small residual thyroid tissue in the neck and a mediastinum lesion, consistent with the thyroid cancer metastatic disease. The uptakes in the stomach and bowel are normal physiologic findings.

History

The history of nuclear medicine is rich with contributions from gifted scientists across different disciplines in physics, chemistry, engineering, and medicine. The multidisciplinary nature of Nuclear Medicine makes it difficult for medical historians to determine the birthdate of Nuclear Medicine. This can probably be best placed between the discovery of artificial radioactivity in 1934 and the production of radionuclides by Oak Ridge National Laboratory for medicine related use, in 1946.^[3]

Many historians consider the discovery of artificially produced radionuclides by Frédéric Joliot-Curie and Irène Joliot-Curie in 1934 as the most significant milestone in Nuclear Medicine.^[3] In February 1934, they reported the first artificial production of radioactive material in the *Nature* journal, after discovering radioactivity in aluminum foil that was irradiated with a polonium preparation. Their work built upon earlier discoveries by Wilhelm Konrad Roentgen for X-ray, Henri Becquerel for radioactive uranium salts, and Marie Curie (mother of Irene Curie) for radioactive thorium, polonium and coining the term "radioactivity." Taro Takemi studied the application of nuclear physics to medicine in the 1930s. The history of Nuclear Medicine will not be complete without mentioning these early pioneers.

Nuclear medicine gained public recognition as a potential specialty on December 7, 1946 when an article was published in the *Journal of the American Medical Association* by Sam Seidlin. The article described a successful treatment of a patient with thyroid cancer metastases using radioiodine (I-131). This is considered by many historians as the most important article ever published in Nuclear Medicine.^[4] Although, the earliest use of I-131 was devoted to therapy of thyroid cancer, its use was later expanded to include imaging of the thyroid gland, quantification of the thyroid function, and therapy for hyperthyroidism.

Widespread clinical use of Nuclear Medicine began in the early 1950s, as knowledge expanded about radionuclides, detection of radioactivity, and using certain radionuclides to trace biochemical processes. Pioneering works by Benedict Cassen in developing the first rectilinear scanner and Hal O. Anger's scintillation camera (Anger camera) broadened the young discipline of Nuclear Medicine into a full-fledged medical imaging specialty.

In these years of Nuclear Medicine, the growth was phenomenal. The Society of Nuclear Medicine was formed in 1954 in Spokane, Washington, USA. In 1960, the Society began publication of the Journal of Nuclear Medicine, the premier scientific journal for the discipline in America. There was a flurry of research and development of new radionuclides and radiopharmaceuticals for use with the imaging devices and for in-vitro studies⁵.

Among many radionuclides that were discovered for medical-use, none were as important as the discovery and development of Technetium-99m. It was first discovered in 1937 by C. Perrier and E. Segre as an artificial element to fill space number 43 in the Periodic Table. The development of generator system to produce Technetium-99m in the 1960s became a practical method for medical use. Today, Technetium-99m is the most utilized element in Nuclear Medicine and is employed in a wide variety of Nuclear Medicine imaging studies.

By the 1970s most organs of the body could be visualized using Nuclear Medicine procedures. In 1971, American Medical Association officially recognized nuclear medicine as a medical specialty.^[5] In 1972, the American Board of Nuclear Medicine was established, cementing Nuclear Medicine as a medical specialty.

In the 1980s, radiopharmaceuticals were designed for use in diagnosis of heart disease. The development of single photon emission tomography, around the same time, led to three-dimensional reconstruction of the heart and establishment of the field of Nuclear Cardiology.

More recent developments in Nuclear Medicine include the invention of the first positron emission tomography scanner (PET). The concept of emission and transmission tomography, later developed into single photon emission computed tomography (SPECT), was introduced by David E. Kuhl and Roy Edwards in the late 1950s. Their work led to the design and construction of several tomographic instruments at the University of Pennsylvania. Tomographic imaging techniques were further developed at the Washington University School of Medicine. These innovations led to fusion imaging with SPECT and CT by Bruce Hasegawa from University of California San Francisco (UCSF), and the first PET/CT prototype by D. W. Townsend from University of Pittsburgh in 1998.

PET and PET/CT imaging experienced slower growth in its early years owing to the cost of the modality and the requirement for an on-site or nearby cyclotron. However, an administrative decision to approve medical reimbursement of limited PET and PET/CT applications in oncology has led to phenomenal growth and widespread acceptance over the last few years. PET/CT imaging is now an integral part of oncology for diagnosis, staging and treatment monitoring.

Source of radionuclides, with notes on a few radiopharmaceuticals

About a third of the world's supply, and most of North America's supply, of medical isotopes are produced at the Chalk River Laboratories in Chalk River, Ontario, Canada. (Another third of the world's supply, and most of Europe's supply, are produced at the Petten nuclear reactor in the Netherlands.) The Canadian Nuclear Safety Commission ordered the NRU reactor to be shut down on November 18, 2007 for regularly scheduled maintenance and an upgrade of the safety systems to modern standards. The upgrade took longer than expected and in December 2007 a critical shortage of medical isotopes occurred. The Canadian government unanimously passed emergency legislation, allowing the reactor to re-start on 16 December 2007, and production of medical isotopes to continue.

The Chalk River reactor is used to irradiate materials with neutrons which are produced in great quantity during the fission of U-235. These neutrons change the nucleus of the irradiated material by adding a neutron, or by splitting it in the process of nuclear fission. In a reactor, one of the fission products of uranium is molybdenum-99 which is extracted and shipped to radiopharmaceutical houses all over North America. The Mo-99 radioactively beta decays with a half-life of 2.7 days, turning initially into Tc-99m, which is then extracted (milked) from a "moly cow" (see technetium-99m generator). The Tc-99m then further decays, while inside a patient, releasing a gamma photon which is detected by the gamma camera. It decays to its ground state of Tc-99, which is relatively non-radioactive compared to Tc-99m.

The most commonly used radioisotope in PET F-18, is not produced in any nuclear reactor, but rather in a circular accelerator called a cyclotron. The cyclotron is used to accelerate protons to bombard the stable heavy isotope of oxygen O-18. The O-18 constitutes about 0.20% of ordinary oxygen (mostly O-16), from which it is extracted. The F-18 is then typically used to make FDG (see this link for more information on this process).

Common isotopes used in nuclear medicine

isotope	symbol	Z	T _{1/2}	decay	photons	β
Imaging:						
fluorine-18	¹⁸ F	9	109.77 m	β ⁺	511 (193%)	0.664 (97%)
gallium-67	⁶⁷ Ga	31	3.26 d	ec	93 (39%), 185 (21%), 300 (17%)	-
krypton-81m	^{81m} Kr	36	13.1 s	IT	190 (68%)	-
rubidium-82	⁸² Rb	37	1.27 m	β ⁺	511 (191%)	3.379 (95%)
technetium-99m	^{99m} Tc	43	6.01 h	IT	140 (89%)	-
indium-111	¹¹¹ In	49	2.80 d	ec	171 (90%), 245 (94%)	-
iodine-123	¹²³ I	53	13.3 h	ec	159 (83%)	-
xenon-133	¹³³ Xe	54	5.24 d	β ⁻	81 (31%)	0.364 (99%)
thallium-201	²⁰¹ Tl	81	3.04 d	ec	69–83* (94%), 167 (10%)	-
Therapy:						
yttrium-90	⁹⁰ Y	39	2.67 d	β ⁻	-	2.280 (100%)
iodine-131	¹³¹ I	53	8.02 d	β ⁻	364 (81%)	0.807 (100%)
Z = atomic number, the number of protons; T _{1/2} = half-life; decay = mode of decay photons = principle photon energies in kilo-electron volts, keV, (abundance/decay) β = beta maximum energy in mega-electron volts, MeV, (abundance/decay) β ⁺ = β ⁺ decay; β ⁻ = β ⁻ decay; IT = isomeric transition; ec = electron capture * X-rays from progeny, mercury, Hg						

A typical nuclear medicine study involves administration of a radionuclide into the body by intravenous injection in liquid or aggregate form, ingestion while combined with food, inhalation as a gas or aerosol, or rarely, injection of a radionuclide that has undergone micro-encapsulation. Some studies require the labeling of a patient's own blood cells with a radionuclide (leukocyte scintigraphy and red blood cell scintigraphy). Most diagnostic radionuclides emit gamma rays, while the cell-damaging properties of beta particles are used in therapeutic applications. Refined radionuclides for use in nuclear medicine are derived from fission or fusion processes in nuclear reactors, which produce radionuclides with longer half-lives, or cyclotrons, which produce radionuclides with shorter half-lives, or take advantage of natural decay processes in dedicated generators, i.e. molybdenum/technetium or strontium/rubidium.

The most commonly used intravenous radionuclides are:

- Technetium-99m (technetium-99m)
- Iodine-123 and 131

- Thallium-201
- Gallium-67
- Fluorine-18 Fluorodeoxyglucose
- Indium-111 Labeled Leukocytes

The most commonly used gaseous/aerosol radionuclides are:

- Xenon-133
- Krypton-81m
- Technetium-99m Technegas^[6]
- Technetium-99m DTPA

Analysis

The end result of the nuclear medicine imaging process is a "dataset" comprising one or more images. In multi-image datasets the array of images may represent a time sequence (i.e. cine or movie) often called a "dynamic" dataset, a cardiac gated time sequence, or a spatial sequence where the gamma-camera is moved relative to the patient. SPECT (single photon emission computed tomography) is the process by which images acquired from a rotating gamma-camera are reconstructed to produce an image of a "slice" through the patient at a particular position. A collection of parallel slices form a slice-stack, a three-dimensional representation of the distribution of radionuclide in the patient.

The nuclear medicine computer may require millions of lines of source code to provide quantitative analysis packages for each of the specific imaging techniques available in nuclear medicine.

Time sequences can be further analysed using kinetic models such as multi-compartment models or a Patlak plot.

Radiation dose

A patient undergoing a nuclear medicine procedure will receive a radiation dose. Under present international guidelines it is assumed that any radiation dose, however small, presents a risk. The radiation doses delivered to a patient in a nuclear medicine investigation present a very small risk of inducing cancer. In this respect it is similar to the risk from X-ray investigations except that the dose is delivered internally rather than from an external source such as an X-ray machine.

The radiation dose from a nuclear medicine investigation is expressed as an effective dose with units of sieverts (usually given in millisieverts, mSv). The effective dose resulting from an investigation is influenced by the amount of radioactivity administered in megabecquerels (MBq), the physical properties of the radiopharmaceutical used, its distribution in the body and its rate of clearance from the body.

Effective doses can range from 6 μ Sv (0.006 mSv) for a 3 MBq chromium-51 EDTA measurement of glomerular filtration rate to 37 mSv for a 150 MBq thallium-201 non-specific tumour imaging procedure. The common bone scan with 600 MBq of technetium-99m-MDP has an effective dose of approximately 3.5 mSv (1).

Formerly, units of measurement were the curie (Ci), being 3.7×10^{10} Bq, and also 1.0 grams of Radium (Ra-226); the rad (radiation absorbed dose), now replaced by the gray; and the rem (Röntgen equivalent man), now replaced with the sievert. The rad and rem are essentially equivalent for almost all nuclear medicine procedures, and only alpha radiation will produce a higher Rem or Sv value, due to its much higher Relative Biological Effectiveness (RBE). Alpha emitters are nowadays rarely used in nuclear medicine, but were used extensively before the advent of nuclear reactor and accelerator produced radionuclides. The concepts involved in radiation exposure to humans is covered by the field of Health Physics.

Nuclear Medicine Careers

Nuclear Medicine Technologist

The information below is adapted from the Society of Nuclear Medicine (SNM) website on a scientist career. For more information and educational requirements, please see training ^[7]

The nuclear medicine scientist works closely with the nuclear medicine physician. Some of the scientist's primary responsibilities are to:

- Prepare and administer radioactive chemical compounds, known as radiopharmaceuticals
- Perform patient imaging procedures using sophisticated radiation-detecting instrumentation
- Accomplish computer processing and image enhancement
- Analyze biologic specimens in the laboratory
- Provide images, data analysis, and patient information to the physician for diagnostic interpretation.

During an imaging procedure, the scientist works directly with the patient. The scientist:

- Gains the patient's confidence by obtaining pertinent history, describing the procedure and answering any questions
- Monitors the patient's physical condition during the course of the procedure
- Notes any specific patient's comments which might indicate the need for additional images or might be useful to the physician in interpreting the results of the procedure.

Nuclear medicine scientists work in a wide variety of clinical settings, such as

- Community hospitals
- University-affiliated teaching hospitals and medical centers
- Outpatient imaging facilities
- Public health institutions
- Government and private research institutes.

The physician career in nuclear medicine

Nuclear medicine physicians are primarily responsible for interpretation of diagnostic nuclear medicine scans and treatment of certain diseases, such as cancer, thyroid disease and palliative bone pain.

There are a variety of reasons why physicians have chosen to specialize in nuclear medicine. Some became nuclear medicine physicians because of their interest in nuclear physics and medical imaging. Others may have switched to nuclear medicine after training in other specialties, because of the regular work hours (on average about 8 to 10 hours a day). Others have chosen nuclear medicine because of research opportunities in molecular medicine or molecular imaging.

Nuclear medicine physicians frequently interact with other specialties in medicine and consult on a variety of clinical cases. A nuclear medicine report may save a patient from more invasive or high risk procedures, and/or lead to early disease diagnosis. Nuclear Medicine physicians can be called upon to consult on complex or equivocal clinical cases. Aside from consultations with other physicians, nuclear physicians may directly interact with patients through various nuclear medicine therapies (e.g.: I131 thyroid therapy, refractory lymphoma treatment, palliative bone pain therapy).

A disadvantage of a nuclear medicine career for a physician is that it suffers from low job turnover and a small job market, owing to the specialized nature of the field. Advantages of the field include job satisfaction and more regular hours than many fields of medicine, since very rarely are the procedures in this field performed on an emergency basis.

Nuclear medicine residency/training (physicians)

The information below is adapted from the American Board of Nuclear Medicine (ABNM). For more information, please see ABNM^[8]

General professional education requirement in the United States of America: graduation from a medical school approved by the Liaison Committee on Medical Education or the American Association of Colleges of Osteopathic Medicine.

In USA the post-doctoral training in nuclear medicine can be approached from three different pathways:

1. If the person has successfully completed an accredited radiology residency then additional ONE year of training in Nuclear Medicine is required to be eligible for ABNM board certification.
2. If the person has successfully completed a clinical residency (e.g. Internal Medicine, Family Medicine, Surgery, Neurology, etc.) then an additional TWO years of training in Nuclear Medicine is required to be eligible for ABNM board certification.
3. If the person has successfully completed one year of preparatory post-doctoral training (internship) then an additional THREE years of training in Nuclear Medicine is required to be eligible for ABNM board certification.

In INDIA the post-doctoral training in nuclear medicine can be approached from three different pathways after completing MBBS (graduation)

1. one can directly appear through MD examination conducted by three institutes. they are AIIMS New Delhi, PGI Chandigarh and SGPGI Lucknow.
2. one can appear in DNB entrance examination and get 3 year residency programme in approved government and private hospitals
3. one can appear through diploma courses to get a 2 year residency programme.

Notes

- [1] thefreedictionary.com > scintigraphy (<http://medical-dictionary.thefreedictionary.com/scintigraphy>) Citing: Dorland's Medical Dictionary for Health Consumers, 2007 by Saunders; Saunders Comprehensive Veterinary Dictionary, 3 ed. 2007; McGraw-Hill Concise Dictionary of Modern Medicine, 2002 by The McGraw-Hill Companies
- [2] [www.molecularimagingcenter.org], Gambhir S. Just what is molecular medicine.
- [3] Edwards CI: Tumor localizing radionuclides in retrospect and prospect. *Semin Nucl Med* 3:186–189, 1979.
- [4] Henkin R. et al: Nuclear Medicine. First edition 1996. ISBN 9780801677014.
- [5] <http://interactive.snm.org/docs/whatisnucmed.pdf> from the Society of Nuclear Medicine.
- [6] <http://jcsmr.anu.edu.au/technegas/home.html>
- [7] Training (<http://interactive.snm.org/index.cfm?PageID=985&RPID=193>)
- [8] Acgme (http://www.acgme.org/acWebsite/navPages/nav_200.asp)

Further reading

- Mas JC: A Patient's Guide to Nuclear Medicine Procedures: English-Spanish. Society of Nuclear Medicine, 2008. ISBN 978-0972647892
- Taylor A, Schuster DM, Naomi Alazraki N: A Clinicians' Guide to Nuclear Medicine, 2nd edition. Society of Nuclear Medicine, 2000. ISBN 978-0932004727
- Mark J. Shumate MJ, Kooby DA, Alazraki NP: A Clinician's Guide to Nuclear Oncology: Practical Molecular Imaging and Radionuclide Therapies. Society of Nuclear Medicine, January 2007. ISBN 978-0972647885
- Ell P, Gambhir S: Nuclear Medicine in Clinical Diagnosis and Treatment. Churchill Livingstone, 2004. (1950 pages) ISBN 978-0443073120

External links

- Society of Nuclear Medicine (<http://www.snm.org/>)
- Brochure: What is Nuclear Medicine? (<http://interactive.snm.org/docs/whatisnucmed.pdf>)
- Resource center: information about nuclear medicine (<http://interactive.snm.org/index.cfm?PageID=6309&RPID=1089>)
- International Atomic Energy Agency (IAEA), Division of Human Health, Nuclear Medicine (<http://www-naweb.iaea.org/nahu/nm/default.asp>)
- RADAR Medical Procedure Radiation Dose Calculator and Consent Language Generator (<http://www.doseinfo-radar.com/RADARDoseRiskCalc.html>)
- Association of Image Producers and Equipment Suppliers (<http://www.aipes-eeig.org/>)

Medical imaging

Medical imaging is the technique and process used to create images of the human body (or parts and function thereof) for clinical purposes (medical procedures seeking to reveal, diagnose or examine disease) or medical science (including the study of normal anatomy and physiology). Although imaging of removed organs and tissues can be performed for medical reasons, such procedures are not usually referred to as medical imaging, but rather are a part of pathology.

As a discipline and in its widest sense, it is part of biological imaging and incorporates radiology (in the wider sense), nuclear medicine, investigative radiological sciences, endoscopy, (medical) thermography, medical photography and microscopy (e.g. for human pathological investigations).

Measurement and recording techniques which are not primarily designed to produce images, such as electroencephalography (EEG), magnetoencephalography (MEG), Electrocardiography (EKG) and others, but which produce data susceptible to be represented as maps (i.e. containing positional information), can be seen as forms of medical imaging.

In 2010, 5 billion medical imaging studies were done worldwide.^[1] Radiation exposure from medical imaging in 2006 made up about 50% of total ionizing radiation exposure in the United States.^[2]

Overview

In the clinical context, "invisible light" medical imaging is generally equated to radiology or "clinical imaging" and the medical practitioner responsible for interpreting (and sometimes acquiring) the images is a radiologist. "Visible light" medical imaging involves digital video or still pictures that can be seen without special equipment. Dermatology and wound care are two modalities that utilize visible light imagery. Diagnostic radiography designates the technical aspects of medical imaging and in particular the acquisition of medical images. The *radiographer* or *radiologic technologist* is usually responsible for acquiring medical images of diagnostic quality, although some radiological interventions are performed by radiologists. While radiology is an evaluation of anatomy, nuclear medicine provides functional assessment.

As a field of scientific investigation, medical imaging constitutes a sub-discipline of biomedical engineering, medical physics or medicine depending on the context: Research and development in the area of instrumentation, image acquisition (e.g. radiography), modelling and quantification are usually the preserve of biomedical engineering, medical physics and computer science; Research into the application and interpretation of medical images is usually the preserve of radiology and the medical sub-discipline relevant to medical condition or area of medical science (neuroscience, cardiology, psychiatry, psychology, etc.) under investigation. Many of the techniques developed for medical imaging also have scientific and industrial applications.

Medical imaging is often perceived to designate the set of techniques that noninvasively produce images of the internal aspect of the body. In this restricted sense, medical imaging can be seen as the solution of mathematical inverse problems. This means that cause (the properties of living tissue) is inferred from effect (the observed signal). In the case of ultrasonography the probe consists of ultrasonic pressure waves and echoes inside the tissue show the internal structure. In the case of projection radiography, the probe is X-ray radiation which is absorbed at different rates in different tissue types such as bone, muscle and fat.

The term noninvasive is a term based on the fact that following medical imaging modalities do not penetrate the skin physically. But on the electromagnetic and radiation level, they are quite invasive. From the high energy photons in X-Ray Computed Tomography, to the 2+ Tesla coils of an MRI device, these modalities alter the physical and chemical environment of the body in order to obtain data.

Radiography

Two forms of radiographic images are in use in medical imaging; projection radiography and fluoroscopy, with the latter being useful for and catheter guidance. These 2D techniques are still in wide use despite the advance of 3D tomography due to the low cost, high resolution, and depending on application, lower radiation dosages. This imaging modality utilizes a wide beam of x rays for image acquisition and is the first imaging technique available in modern medicine.

- *Fluoroscopy* produces real-time images of internal structures of the body in a similar fashion to radiography, but employs a constant input of x-rays, at a lower dose rate. Contrast media, such as barium, iodine, and air are used to visualize internal organs as they work. Fluoroscopy is also used in image-guided procedures when constant feedback during a procedure is required. An image receptor is required to convert the radiation into an image after it has passed through the area of interest. Early on this was a fluorescing screen, which gave way to an Image Amplifier (IA) which was a large vacuum tube that had the receiving end coated with cesium iodide, and a mirror at the opposite end. Eventually the mirror was replaced with a TV camera.
 - *Projectional radiographs*, more commonly known as x-rays, are often used to determine the type and extent of a fracture as well as for detecting pathological changes in the lungs. With the use of radio-opaque contrast media, such as barium, they can also be used to visualize the structure of the stomach and intestines - this can help diagnose ulcers or certain types of colon cancer.
-

Magnetic resonance imaging (MRI)

A magnetic resonance imaging instrument (MRI scanner), or "nuclear magnetic resonance (NMR) imaging" scanner as it was originally known, uses powerful magnets to polarise and excite hydrogen nuclei (single proton) in water molecules in human tissue, producing a detectable signal which is spatially encoded, resulting in images of the body. MRI uses three electromagnetic fields: a very strong (on the order of units of teslas) static magnetic field to polarize the hydrogen nuclei, called the static field; a weaker time-varying (on the order of 1 kHz) field(s) for spatial encoding, called the gradient field(s); and a weak radio-frequency (RF) field for manipulation of the hydrogen nuclei to produce measurable signals, collected through an RF antenna.

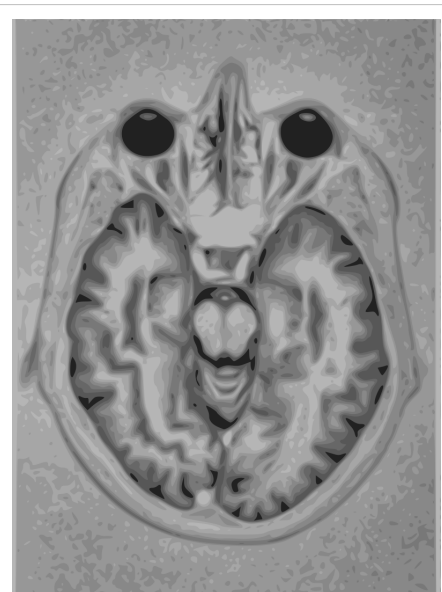
Like CT, MRI traditionally creates a two dimensional image of a thin "slice" of the body and is therefore considered a tomographic imaging technique. Modern MRI instruments are capable of producing images in the form of 3D blocks, which may be considered a generalisation of the single-slice, tomographic, concept. Unlike CT, MRI does not involve the use of ionizing radiation and is therefore not associated with the same health hazards. For example, because MRI has only been in use since the early 1980s, there are no known long-term effects of exposure to strong static fields (this is the subject of some debate; see 'Safety' in MRI) and therefore there is no limit to the number of scans to which an individual can be subjected, in contrast with X-ray and CT. However, there are well-identified health risks associated with tissue heating from exposure to the RF field and the presence of implanted devices in the body, such as pace makers. These risks are strictly controlled as part of the design of the instrument and the scanning protocols used.

Because CT and MRI are sensitive to different tissue properties, the appearance of the images obtained with the two techniques differ markedly. In CT, X-rays must be blocked by some form of dense tissue to create an image, so the image quality when looking at soft tissues will be poor. In MRI, while any nucleus with a net nuclear spin can be used, the proton of the hydrogen atom remains the most widely used, especially in the clinical setting, because it is so ubiquitous and returns a large signal. This nucleus, present in water molecules, allows the excellent soft-tissue contrast achievable with MRI.

Nuclear medicine

Nuclear medicine encompasses both diagnostic imaging and treatment of disease, and may also be referred to as molecular medicine or molecular imaging & therapeutics^[3]. Nuclear medicine uses certain properties of isotopes and the energetic particles emitted from radioactive material to diagnose or treat various pathology. Different from the typical concept of anatomic radiology, nuclear medicine enables assessment of physiology. This function-based approach to medical evaluation has useful applications in most subspecialties, notably oncology, neurology, and cardiology. *Gamma cameras* are used in e.g. scintigraphy, SPECT and PET to detect regions of biologic activity that may be associated with disease. Relatively short lived isotope, such as ^{123}I is administered to the patient. Isotopes are often preferentially absorbed by biologically active tissue in the body, and can be used to identify tumors or fracture points in bone. Images are acquired after collimated photons are detected by a crystal that gives off a light signal, which is in turn amplified and converted into count data.

- *Scintigraphy* ("scint") is a form of diagnostic test wherein radioisotopes are taken internally, for example intravenously or orally. Then, gamma cameras capture and form two-dimensional^[4] images from the radiation emitted by the radiopharmaceuticals.



A brain MRI representation

- *SPECT* is a 3D tomographic technique that uses gamma camera data from many projections and can be reconstructed in different planes. A dual detector head gamma camera combined with a CT scanner, which provides localization of functional SPECT data, is termed a SPECT/CT camera, and has shown utility in advancing the field of molecular imaging. In most other medical imaging modalities, energy is passed through the body and the reaction or result is read by detectors. In SPECT imaging, the patient is injected with a radioisotope, most commonly Thallium 201TI, Technetium 99mTC, Iodine 123I, and Gallium 67Ga^[5]
- . The radioactive gamma rays are emitted through the body as the natural decaying process of these isotopes takes place. The emissions of the gamma rays are captured by detectors that surround the body. This essentially means that the human is now the source of the radioactivity, rather than the medical imaging devices such as X-Ray, CT, or Ultrasound.
- *Positron emission tomography* (PET) uses coincidence detection to image functional processes. Short-lived positron emitting isotope, such as ¹⁸F, is incorporated with an organic substance such as glucose, creating F18-fluorodeoxyglucose, which can be used as a marker of metabolic utilization. Images of activity distribution throughout the body can show rapidly growing tissue, like tumor, metastasis, or infection. PET images can be viewed in comparison to computed tomography scans to determine an anatomic correlate. Modern scanners combine PET with a CT, or even MRI, to optimize the image reconstruction involved with positron imaging. This is performed on the same equipment without physically moving the patient off of the gantry. The resultant hybrid of functional and anatomic imaging information is a useful tool in non-invasive diagnosis and patient management.

Photoacoustic imaging

Photoacoustic imaging is a recently developed hybrid biomedical imaging modality based on the photoacoustic effect. It combines the advantages of optical absorption contrast with ultrasonic spatial resolution for deep imaging in (optical) diffusive or quasi-diffusive regime. Recent studies have shown that photoacoustic imaging can be used in vivo for tumor angiogenesis monitoring, blood oxygenation mapping, functional brain imaging, and skin melanoma detection, etc.

Breast Thermography

Digital infrared imaging thermography is based on the principle that metabolic activity and vascular circulation in both pre-cancerous tissue and the area surrounding a developing breast cancer is almost always higher than in normal breast tissue. Cancerous tumors require an ever-increasing supply of nutrients and therefore increase circulation to their cells by holding open existing blood vessels, opening dormant vessels, and creating new ones (neovascularization). This process frequently results in an increase in regional surface temperatures of the breast. Digital infrared imaging uses extremely sensitive medical infrared cameras and sophisticated computers to detect, analyze, and produce high-resolution diagnostic images of these temperature variations. Because of DII's sensitivity, these temperature variations may be among the earliest signs of breast cancer and/or a pre-cancerous state of the breast^[6].

Tomography

Tomography is the method of imaging a single plane, or slice, of an object resulting in a tomogram. There are several forms of tomography:

- **Linear tomography:** This is the most basic form of tomography. The X-ray tube moved from point "A" to point "B" above the patient, while the cassette holder (or "bucky") moves simultaneously under the patient from point "B" to point "A." The fulcrum, or pivot point, is set to the area of interest. In this manner, the points above and below the focal plane are blurred out, just as the background is blurred when panning a camera during exposure. No longer carried out and replaced by computed tomography.

- Poly tomography: This was a complex form of tomography. With this technique, a number of geometrical movements were programmed, such as hypocycloidic, circular, figure 8, and elliptical. Philips Medical Systems [7] produced one such device called the 'Polytome.' This unit was still in use into the 1990s, as its resulting images for small or difficult physiology, such as the inner ear, was still difficult to image with CTs at that time. As the resolution of CTs got better, this procedure was taken over by the CT.
 - Zonography: This is a variant of linear tomography, where a limited arc of movement is used. It is still used in some centres for visualising the kidney during an intravenous urogram (IVU).
 - Orthopantomography (OPT or OPG): The only common tomographic examination in use. This makes use of a complex movement to allow the radiographic examination of the mandible, as if it were a flat bone. It is often referred to as a "Panorex", but this is incorrect, as it is a trademark of a specific company.
 - Computed Tomography (CT), or Computed Axial Tomography (CAT: A CT scan, also known as a CAT scan), is a helical tomography (latest generation), which traditionally produces a 2D image of the structures in a thin section of the body. It uses X-rays. It has a greater ionizing radiation dose burden than projection radiography; repeated scans must be limited to avoid health effects. CT is based on the same principles as X-Ray projections but in this case, the patient is enclosed in a surrounding ring of detectors assigned with 500-1000 scintillation detectors^[5]
- . This being the fourth-generation X-Ray CT scanner geometry. Previously in older generation scanners, the X-Ray beam was paired by a translating source and detector.

Ultrasound

Medical ultrasonography uses high frequency broadband sound waves in the megahertz range that are reflected by tissue to varying degrees to produce (up to 3D) images. This is commonly associated with imaging the fetus in pregnant women. Uses of ultrasound are much broader, however. Other important uses include imaging the abdominal organs, heart, breast, muscles, tendons, arteries and veins. While it may provide less anatomical detail than techniques such as CT or MRI, it has several advantages which make it ideal in numerous situations, in particular that it studies the function of moving structures in real-time, emits no ionizing radiation, and contains speckle that can be used in elastography. Ultrasound is also used as a popular research tool for capturing raw data, that can be made available through an Ultrasound research interface, for the purpose of tissue characterization and implementation of new image processing techniques. The concepts of ultrasound differ from other medical imaging modalities in the fact that it is operated by the transmission and receipt of sound waves. The high frequency sound waves are sent into the tissue and depending on the composition of the different tissues; the signal will be attenuated and returned at separate intervals. A path of reflected sound waves in a multilayered structure can be defined by an input acoustic impedance(Ultrasound sound wave) and the Reflection and transmission coefficients of the relative structures^[5]. It is very safe to use and does not appear to cause any adverse effects, although information on this is not well documented. It is also relatively inexpensive and quick to perform. Ultrasound scanners can be taken to critically ill patients in intensive care units, avoiding the danger caused while moving the patient to the radiology department. The real time moving image obtained can be used to guide drainage and biopsy procedures. Doppler capabilities on modern scanners allow the blood flow in arteries and veins to be assessed.

Medical imaging topics

Maximizing imaging procedure use

The amount of data obtained in a single MR or CT scan is very extensive. Some of the data that radiologists discard could save patients time and money, while reducing their exposure to radiation and risk of complications from invasive procedures.^[8]

Creation of three-dimensional images

Recently, techniques have been developed to enable CT, MRI and ultrasound scanning software to produce 3D images for the physician.^[9] Traditionally CT and MRI scans produced 2D static output on film. To produce 3D images, many scans are made, then combined by computers to produce a 3D model, which can then be manipulated by the physician. 3D ultrasounds are produced using a somewhat similar technique. In diagnosing disease of the viscera of abdomen, ultrasound is particularly sensitive on imaging of biliary tract, urinary tract and female reproductive organs (ovary, fallopian tubes). As for example, diagnosis of gall stone by dilatation of common bile duct and stone in common bile duct. With the ability to visualize important structures in great detail, 3D visualization methods are a valuable resource for the diagnosis and surgical treatment of many pathologies. It was a key resource for the famous, but ultimately unsuccessful attempt by Singaporean surgeons to separate Iranian twins Ladan and Laleh Bijani in 2003. The 3D equipment was used previously for similar operations with great success.

Other proposed or developed techniques include:

- Diffuse optical tomography
- Elastography
- Electrical impedance tomography
- Optoacoustic imaging
- Ophthalmology
 - A-scan
 - B-scan
 - Corneal topography
 - Optical coherence tomography
 - Scanning laser ophthalmoscopy

Some of these techniques are still at a research stage and not yet used in clinical routines.

Compression of medical images

Medical imaging techniques produce very large amounts of data, especially from CT, MRI and PET modalities. As a result, storage and communications of electronic image data are prohibitive without the use of compression. JPEG 2000 is the state-of-the-art image compression DICOM standard for storage and transmission of medical images. The cost and feasibility of accessing large image data sets over low or various bandwidths are further addressed by use of another DICOM standard, called JPIP, to enable efficient streaming of the JPEG 2000 compressed image data.

Non-diagnostic imaging

Neuroimaging has also been used in experimental circumstances to allow people (especially disabled persons) to control outside devices, acting as a brain computer interface.

Archiving and recording

Used primarily in ultrasound imaging, capturing the image a medical imaging device is required for archiving and telemedicine applications. In most scenarios, a frame grabber is used in order to capture the video signal from the medical device and relay it to a computer for further processing and operations.^[10]

Open source software for medical image analysis

Several open source software packages are available for performing analysis of medical images:

- ImageJ
- 3D Slicer
- ITK
- OsiriX
- GemIdent
- MicroDicom
- FreeSurfer

Use in pharmaceutical clinical trials

Medical imaging has become a major tool in clinical trials since it enables rapid diagnosis with visualization and quantitative assessment.

A typical clinical trial goes through multiple phases and can take up to eight years. Clinical endpoints or outcomes are used to determine whether the therapy is safe and effective. Once a patient reaches the endpoint, he/she is generally excluded from further experimental interaction. Trials that rely solely on clinical endpoints are very costly as they have long durations and tend to need large number of patients.

In contrast to clinical endpoints, surrogate endpoints have been shown to cut down the time required to confirm whether a drug has clinical benefits. Imaging biomarkers (a characteristic that is objectively measured by an imaging technique, which is used as an indicator of pharmacological response to a therapy) and surrogate endpoints have shown to facilitate the use of small group sizes, obtaining quick results with good statistical power.^[11]

Imaging is able to reveal subtle change that is indicative of the progression of therapy that may be missed out by more subjective, traditional approaches. Statistical bias is reduced as the findings are evaluated without any direct patient contact.

For example, measurement of tumour shrinkage is a commonly used surrogate endpoint in solid tumour response evaluation. This allows for faster and more objective assessment of the effects of anticancer drugs. In evaluating the extent of Alzheimer's disease, it is still prevalent to use behavioural and cognitive tests. MRI scans on the entire brain can accurately pinpoint hippocampal atrophy rate while PET scans is able to measure the brain's metabolic activity by measuring regional glucose metabolism.^[11]

An imaging-based trial will usually be made up of three components:

1. A realistic imaging protocol. The protocol is an outline that standardizes (as far as practically possible) the way in which the images are acquired using the various modalities (PET, SPECT, CT, MRI). It covers the specifics in which images are to be stored, processed and evaluated.
2. An imaging centre that is responsible for collecting the images, perform quality control and provide tools for data storage, distribution and analysis. It is important for images acquired at different time points are displayed in a standardised format to maintain the reliability of the evaluation. Certain specialised imaging contract research

organizations provide to end medical imaging services, from protocol design and site management through to data quality assurance and image analysis.

3. Clinical sites that recruit patients to generate the images to send back to the imaging centre.

See also

- Preclinical imaging
- Cardiac PET
- Biomedical informatics
- Digital Imaging and Communications in Medicine
- Digital mammography
- EMMI European Master in Molecular Imaging
- eMix
- Fotofinder
- Full-body scan
- VoluMedic
- Magnetic field imaging
- Medical examination
- Medical radiography
- Medical test
- Neuroimaging
- Non-invasive (medical)
- PACS
- JPEG 2000 compression
- JPIP streaming
- Pneumoencephalogram
- Radiology information system
- Segmentation (image processing)
- Signal-to-noise ratio
- Society for Imaging Science and Technology
- Tomogram
- Virtopsy

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- Using JPIP for Standard-Compliant Sharing of Medical Image Data (http://www.aware.com/imaging/whitepapers/wp_jpipwado.htm) a white paper by Aware Inc. (<http://www.aware.com/imaging/whitepapers.htm>)

External links

- Medical imaging (<http://www.dmoz.org/Health/Medicine/Imaging/>) at the Open Directory Project
- Medical Image Database (<http://rad.usuhs.edu/medpix/index.html?>) Free Indexed Online Images
- <http://www.aware.com/imaging/accuradjpg.htm> What is JPIP?
- Kromek Ltd (http://www.kromek.com/industries_medical.asp?Ident=311Scanner#Ident)
- Medical Plus Pty Ltd (<http://www.medicalplus-vet.com#Ident>)
- IPRG (<http://www.iprg.co.in/>) Open group related to image processing research resources

Radiology

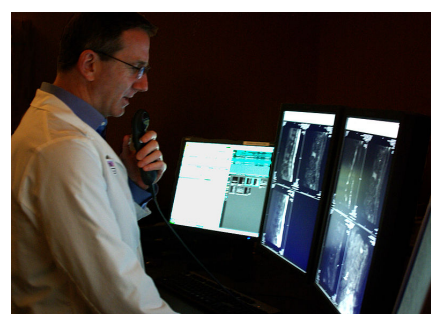
Radiology is the branch of medicine in which physicians visualize the interior of the human body using various forms of radiation. Radiologists utilize an array of imaging technologies (such as ultrasound, computed tomography (CT), nuclear medicine, positron emission tomography (PET) and magnetic resonance imaging (MRI)) to diagnose or treat diseases. Interventional radiology is the performance of (usually minimally invasive) medical procedures with the guidance of imaging technologies. The acquisition of medical imaging is usually carried out by the radiographer or radiologic technologist.

Acquisition of radiological images

The following imaging modalities are used in the field of diagnostic radiology:

Projection (plain) radiography

Radiographs (or roentgenographs, named after the discoverer of x-rays, Wilhelm Conrad Röntgen) are produced by the transmission of x-rays through a patient to a capture device then converted into an image for diagnosis. The original and still common imaging produces silver preganated films. In Film-Screen radiography an x-ray tube generates a beam of x-rays which is aimed at the patient. The x-rays which pass through the patient are filtered to reduce scatter and noise and then strike an undeveloped film, held tight to a screen of light emitting phosphors in a light-tight cassette. The film is then developed chemically and an image appears on the film. Now replacing Film-Screen radiography is Digital Radiography, DR, in which x-rays strike a plate of sensors which then converts the signals generated into digital information and an image on computer screen. Plain radiography was the only imaging modality available during the first 50 years of radiology. It is still the first study ordered in evaluation of the lungs, heart and skeleton because of its wide availability, speed and relative low cost.



A radiologist interprets medical images on a modern Picture archiving and communication system (PACS) workstation. San Diego, CA, 2010.



Madura Foot X-Ray

Fluoroscopy

Fluoroscopy and angiography are special applications of X-ray imaging, in which a fluorescent screen and image intensifier tube is connected to a closed-circuit television system.^{[1] :26} This allows real-time imaging of structures in motion or augmented with a radiocontrast agent. Radiocontrast agents are administered, often swallowed or injected into the body of the patient, to delineate anatomy and functioning of the blood vessels, the genitourinary system or the gastrointestinal tract. Two radiocontrasts are presently in use. Barium (as BaSO_4) may be given orally or rectally for evaluation of the GI tract. Iodine, in multiple proprietary forms, may be given by oral, rectal, intraarterial or intravenous routes. These radiocontrast agents strongly absorb or scatter X-ray radiation, and in conjunction with the real-time imaging allows demonstration of dynamic processes, such as peristalsis in the digestive tract or blood flow in arteries and veins. Iodine contrast may also be concentrated in abnormal areas more or less than in normal tissues and make abnormalities (tumors, cysts, inflammation) more conspicuous. Additionally, in specific circumstances air can be used as a contrast agent for the gastrointestinal system and carbon dioxide can be used as a contrast agent in the venous system; in these cases, the contrast agent attenuates the X-ray radiation less than the surrounding tissues.

Interventional radiology

Interventional radiology (abbreviated **IR** or sometimes **VIR** for **vascular and interventional radiology**, also known as Surgical Radiology or Image-Guided Surgery) is a subspecialty of radiology in which minimally invasive procedures are performed using **image guidance**. Some of these procedures are done for purely diagnostic purposes (e.g., angiogram), while others are done for treatment purposes (e.g., angioplasty).

The basic concept behind interventional radiology is to diagnose or treat pathology, with the most minimally invasive technique possible. Interventional radiologists diagnose and treat several disorders including peripheral vascular disease, renal artery stenosis, inferior vena cava filter placement, gastrostomy tube placements, biliary stents and hepatic interventions. Images are used for guidance and the primary instruments used during the procedure are needles and tiny tubes called catheters. The images provide road maps that allow the interventional radiologist to guide these instruments through the body to the areas containing disease. By minimizing the physical trauma to the patient, peripheral interventions can reduce infection rates and recovery time as well as shorten hospital stays. To be a trained interventionalist in the United States, an individual typically requires fifteen years of post-high school training, of which seven years is spent in residency.^[2]

CT scanning

CT imaging uses X-rays in conjunction with computing algorithms to image the body.^[3] In CT, an X-ray generating tube opposite an X-ray detector (or detectors) in a ring shaped apparatus rotate around a patient producing a computer generated cross-sectional image (tomogram). CT is acquired in the axial plane, while coronal and sagittal images can be rendered by computer reconstruction. Radiocontrast agents are often used with CT for enhanced delineation of anatomy. Although radiographs provide higher spatial resolution, CT can detect more subtle variations in attenuation of X-rays. CT exposes the patient to more ionizing radiation than a radiograph.

Spiral Multi-detector CT utilizes 8, 16, 64 or more detectors during continuous motion of the patient through the radiation beam to obtain much finer detail images in a shorter exam time. With rapid administration of IV contrast during the CT scan these fine detail images can be reconstructed into 3D images of carotid, cerebral and coronary arteries, CTA, CT angiography.



CT scanning has become the test of choice in diagnosing some urgent and emergent conditions such as cerebral hemorrhage, pulmonary embolism (clots in the arteries of the lungs), aortic dissection (tearing of the aortic wall), appendicitis, diverticulitis, and obstructing kidney stones. Continuing improvements in CT technology including faster scanning times and improved resolution have dramatically increased the accuracy and usefulness of CT scanning and consequently increased utilization in medical diagnosis.

The first commercially viable CT scanner was invented by Sir Godfrey Hounsfield at EMI Central Research Labs, Great Britain in 1972. EMI owned the distribution rights to The Beatles music and it was their profits which funded the research.^[4] Sir Hounsfield and Alan McLeod McCormick shared the Nobel Prize for Medicine in 1979 for the invention of CT scanning. The first CT scanner in North America was installed at the Mayo Clinic in Rochester, MN in 1972.

Ultrasound

Medical ultrasonography uses ultrasound (high-frequency sound waves) to visualize soft tissue structures in the body in real time. No ionizing radiation is involved, but the quality of the images obtained using ultrasound is highly dependent on the skill of the person (ultrasonographer) performing the exam. Ultrasound is also limited by its inability to image through air (lungs, bowel loops) or bone. The use of ultrasound in medical imaging has developed mostly within the last 30 years. The first ultrasound images were static and two dimensional (2D), but with modern-day ultrasonography 3D reconstructions can be observed in real-time; effectively becoming 4D.

Because ultrasound does not utilize ionizing radiation, unlike radiography, CT scans, and nuclear medicine imaging techniques, it is generally considered safer. For this reason, this modality plays a vital role in obstetrical imaging. Fetal anatomic development can be thoroughly evaluated allowing early diagnosis of many fetal anomalies. Growth can be assessed over time, important in patients with chronic disease or gestation-induced disease, and in multiple gestations (twins, triplets etc.). Color-Flow Doppler Ultrasound measures the severity of peripheral vascular disease and is used by Cardiology for dynamic evaluation of the heart, heart valves and major vessels. Stenosis of the carotid arteries can presage cerebral infarcts (strokes). DVT in the legs can be found via ultrasound before it dislodges and travels to the lungs (pulmonary embolism), which can be fatal if left untreated. Ultrasound is useful for image-guided interventions like biopsies and drainages such as thoracentesis). Small portable ultrasound devices now replace peritoneal lavage in the triage of trauma victims by directly assessing for the presence of hemorrhage in the peritoneum and the integrity of the major viscera including the liver, spleen and kidneys. Extensive hemoperitoneum (bleeding inside the body cavity) or injury to the major organs may require emergent surgical exploration and repair.

MRI (Magnetic Resonance Imaging)

MRI uses strong magnetic fields to align atomic nuclei (usually hydrogen protons) within body tissues, then uses a radio signal to disturb the axis of rotation of these nuclei and observes the radio frequency signal generated as the nuclei return to their baseline states plus all surrounding areas. The radio signals are collected by small antennae, called coils, placed near the area of interest. An advantage of MRI is its ability to produce images in axial, coronal, sagittal and multiple oblique planes with equal ease. MRI scans give the best soft tissue contrast of all the imaging modalities. With advances in scanning speed and spatial resolution, and improvements in computer 3D algorithms and hardware, MRI has become a tool in musculoskeletal radiology and neuroradiology.



MRI image of human knee with a displaced patella

One disadvantage is that the patient has to hold still for long periods of time in a noisy, cramped space while the imaging is performed. Claustrophobia severe enough to terminate the MRI exam is reported in up to 5% of patients. Recent improvements in magnet design including stronger magnetic fields (3 teslas), shortening exam times, wider, shorter magnet bores and more open magnet designs, have brought some relief for claustrophobic patients. However, in magnets of equal field strength there is often a trade-off between image quality and open design. MRI has great benefit in imaging the brain, spine, and musculoskeletal system. The modality is currently contraindicated for patients with pacemakers, cochlear implants, some indwelling medication pumps, certain types of cerebral aneurysm clips, metal fragments in the eyes and some metallic hardware due to the powerful magnetic fields and strong fluctuating radio signals the body is exposed to. Areas of potential advancement include functional imaging, cardiovascular MRI, as well as MR image guided therapy.

Nuclear Medicine

Nuclear medicine imaging involves the administration into the patient of radiopharmaceuticals consisting of substances with affinity for certain body tissues labeled with radioactive tracer. The most commonly used tracers are Technetium-99m, Iodine-123, Iodine-131, Gallium-67 and Thallium-201 and 18F-FDG. The heart, lungs, thyroid, liver, gallbladder, and bones are commonly evaluated for particular conditions using these techniques. While anatomical detail is limited in these studies, nuclear medicine is useful in displaying physiological function. The excretory function of the kidneys, iodine concentrating ability of the thyroid, blood flow to heart muscle, etc. can be measured. The principal imaging device is the gamma camera which detects the radiation emitted by the tracer in the body and displays it as an image. With computer processing, the information can be displayed as axial, coronal and sagittal images (SPECT images, single-photon emission computed tomography). In the most modern devices Nuclear Medicine images can be fused with a CT scan taken quasi-simultaneously so that the physiological information can be overlaid or co-registered with the anatomical structures to improve diagnostic accuracy.

Positron emission tomography (PET), scanning is a nuclear medicine procedure that deals with positrons. The positrons annihilate to produce two opposite traveling gamma rays to be detected coincidentally, thus improving resolution. In PET scanning, a radioactive, biologically active substance, most often Fludeoxyglucose (18F), is injected into a patient and the radiation emitted by the patient is detected to produce multi-planar images of the body. Metabolically more active tissues, such as cancer, concentrate the active substance more than normal tissues. PET images can be combined (or "fused") with an anatomic imaging study (currently generally CT images), to more accurately localize PET findings and thereby improve diagnostic accuracy.

The fusion technology has gone further to combine PET and MRI similar to PET and CT. PET/MRI fusion will play a crucial role in fine detail of brain imaging, breast cancer screening and small joint imaging of foot. The technology recently came out of a big technical hurdle of altered positron movement in strong magnetic field thus affecting the resolution of PET images and attenuation correction. Siemens is going to showcase the 1st PET/MRI scanner at 2010 RSNA.

Teleradiology

Teleradiology is the transmission of radiographic images from one location to another for interpretation by a radiologist. It is most often used to allow rapid interpretation of emergency room, ICU and other emergent examinations after hours of usual operation, at night and on weekends. In these cases the images are often sent across time zones (i.e. to Spain, Australia, India) with the receiving radiologist working his normal daylight hours. Teleradiology can also be utilized to obtain consultation with an expert or sub-specialist about a complicated or puzzling case.

Teleradiology requires a sending station, high speed Internet connection and high quality receiving station. At the transmission station, plain radiographs are passed through a digitizing machine before transmission, while CT scans, MRIs, Ultrasounds and Nuclear Medicine scans can be sent directly as they are already a stream of digital data. The

computer at the receiving end will need to have a high-quality display screen that has been tested and cleared for clinical purposes. The interpreting radiologist then faxes or e-mails the radiology report to the requesting physician.

The major advantage of teleradiology is the ability to utilize different time zones to provide real-time emergency radiology services around-the-clock. The disadvantages include higher costs, limited contact between the ordering physician and the radiologist, and the inability to cover for procedures requiring an onsite radiologist. Laws and regulations concerning the use of teleradiology vary among the states, with some states requiring a license to practice medicine in the state sending the radiologic exam. Some states require the teleradiology report to be preliminary with the official report issued by a hospital staff radiologist.

Radiologist training

United States

Radiology is a competitive field in medicine and successful applicants are often near the top of their medical school class, with high board scores. The field is rapidly expanding due to advances in computer technology, which is closely linked to modern imaging. Diagnostic radiologists must complete at least 13 years of post-high school education, including 4 years of prerequisite undergraduate training, 4 years of medical school, and 5 years of post-graduate training. The first postgraduate year is usually a transitional year of various rotations, but is sometimes a preliminary internship in medicine or surgery. A four-year diagnostic radiology residency follows. The Radiology resident must pass a medical physics board exam covering the science and technology of ultrasound, CTs, x-rays, nuclear medicine and MRI. Core knowledge of the radiologist includes radiobiology, which is the study of the effects of ionizing radiation on living tissue. Near the completion of residency, the radiologist in training is eligible to take the written and oral board examinations administered by the American Board of Radiology (ABR). The ABR is the most prominent certification for Radiology, however there are other institutions who offer radiology certification such as the American Osteopathic Board of Radiology (AOBR) and the American Board of Physician Specialties (ABPS). Starting in 2010, the ABR's oral board examination structure will be changed to include two computer-based exams, one given after the third year of residency training, and the second given 18 months after the first oral exam. To complete the oral section of the ABR certification, a Radiologist must pass each of the eleven sections. An applicant must pass at least eight of the eleven sections of the ABR oral boards in order to be considered "conditioned" and able to retake the last three or less sections again at a later date to become ABR certified. In order to receive a state medical license, many states now require radiologists to recertify in radiology if their initial or last certification was more than ten years from their medical licensure application date.

Following completion of residency training, radiologists either begin practicing or enter into sub-specialty training programs known as fellowships. Examples of sub-specialty training in radiology include abdominal imaging, thoracic imaging, cross sectional/ultrasound, MRI, musculoskeletal imaging, interventional radiology, neuroradiology, interventional neuroradiology, paediatric radiology, nuclear medicine, emergency radiology, breast imaging and women's imaging. Fellowship training programs in radiology are usually 1 or 2 years in length.^[5]

Radiographic exams are usually performed by radiologic technologists, (also known as diagnostic radiographers) who in the United States have a 2-year Associates Degree and the UK a 3 year Honours Degree.

Veterinary radiologists are veterinarians that specialize in the use of X-rays, ultrasound, MRI and nuclear medicine for diagnostic imaging or treatment of disease in animals. They are certified in either diagnostic radiology or radiation oncology by the American College of Veterinary Radiology.

Germany

After obtaining medical licensure, German radiologists complete a 5-year residency, culminating with a board examination (known as Facharztprüfung).

Italy

Until 2008, a Radiology training program had a duration of four years. At present, a radiology training program lasts five years. Further training is required for specialization in radiotherapy or nuclear medicine.

References

- [1] Novelline, Robert. *Squire's Fundamentals of Radiology*. Harvard University Press. 5th edition. 1997. ISBN 0-674-83339-2.
- [2] Society of Interventional Radiology -- Global Statement Defining Interventional radiology. http://www.sirweb.org/news/newsPDF/IR_Global_Statement.pdf
- [3] Herman, G. T., *Fundamentals of computerized tomography: Image reconstruction from projection*, 2nd edition, Springer, 2009
- [4] Filler, Aaron (2010). "The History, Development and Impact of Computed Imaging in Neurological Diagnosis and Neurosurgery: CT, MRI, and DTI". *Internet Journal of Neurosurgery* (http://www.ispub.com/journal/the_internet_journal_of_neurosurgery/volume_7_number_1_39/article/the-history-development-and-impact-of-computed-imaging-in-neurological-diagnosis-and-neurosurgery-ct-mri-and-dti.html) **7** (1).
- [5] <http://www.healthsystem.virginia.edu/internet/radiology/educ-opps/fellowships.cfm>

External links

- RSNA.org (<http://www.rsna.org>) Radiological Society of North America. Radiology Continued Education and Research.
- ACR.org (<http://www.acr.org>) National Guidelines for Use of Imaging Technologies and Radiology Jobs
- Trinitymed.net (<http://www.trinitymed.net/index-1.html>) National Radiology Market / Career Information and Radiology Jobs
- Radiology (http://www.dmoz.org/Health/Medicine/Medical_Specialties/Radiology/) at the Open Directory Project
- MedPix medical imaging database (<http://rad.usuhs.edu/medpix/medpix.html?mode=default>)
- MedWorm (<http://www.medworm.com/rss/Radiology-37.php>) Radiology directory
- MyPACS medical imaging database (<http://mypacs.net>)
- Radiolopolis (<http://www.Radiolopolis.com>) an international Radiology community for education, research and clinical practice
- radRounds Radiology Network (<http://www.radrounds.com>) - Professional and Social Network for Radiology
- DSCT.com (<http://www.dsct.com>) international dual source CT experts community for education, research and clinical practice

Bold text

Amino acids

Amino acids are molecules containing an amine group, a carboxylic acid group and a side chain that varies between different amino acids. The key elements of an amino acid are carbon, hydrogen, oxygen, and nitrogen. They are particularly important in biochemistry, where the term usually refers to *alpha-amino acids*.

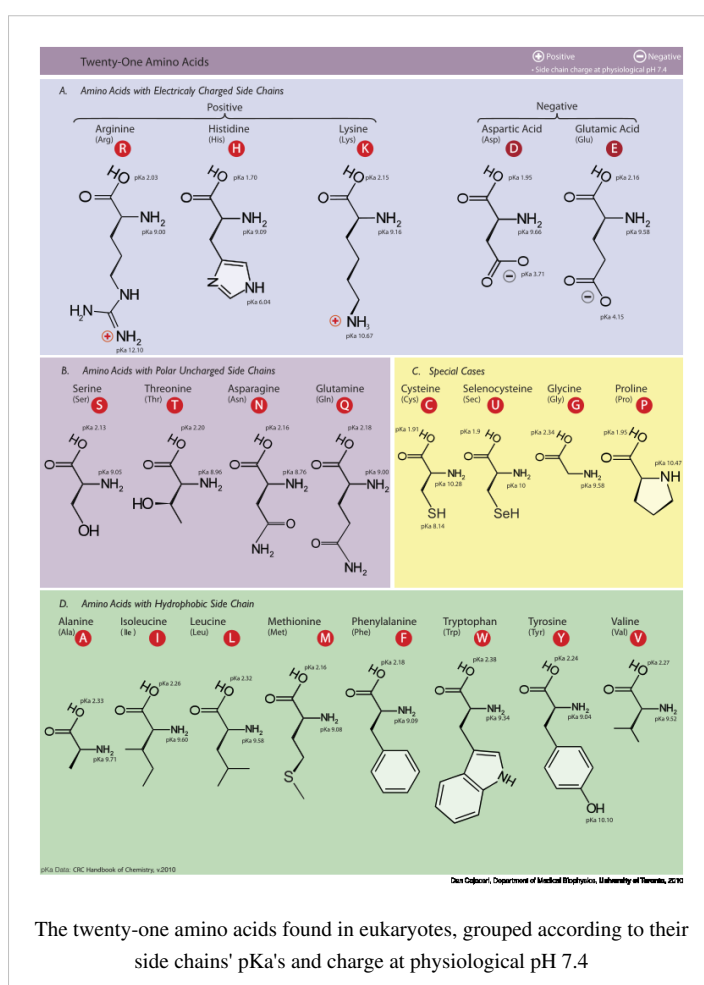
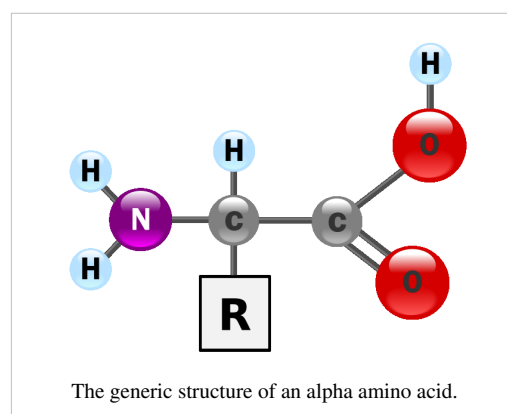
An alpha-amino acid has the generic formula $\text{H}_2\text{NCH(R)COOH}$, where R is an organic substituent^[1]; the amino group is attached to the carbon atom immediately adjacent to the carboxylate group (the α -carbon). Other types of amino acid exist when the amino group is attached to a different carbon atom; for example, in gamma-amino acids (such as gamma-amino-butyric acid) the carbon atom to which the amino group attaches is separated from the carboxylate group by two other carbon atoms. The various alpha-amino acids differ in which side chain (R-group) is attached to their alpha carbon, and can vary in size from just one hydrogen atom in glycine to a large heterocyclic group in tryptophan.

Amino acids are critical to life, and have many functions in metabolism. One particularly important function is to serve as the building blocks of proteins, which are simply linear chains of amino acids. Just as the letters of the alphabet can be combined to form an almost endless variety of words, amino acids can be linked together in varying sequences to form a vast variety of proteins.^[2]

Due to their central role in biochemistry, amino acids are important in nutrition and are commonly used in food technology and industry. For example, monosodium glutamate is a common flavor enhancer that gives food the taste *umami*. In industry, applications include the production of biodegradable plastics, drugs, and chiral catalysts.

History

The first few amino acids were discovered in the early 19th century. In 1806, the French chemists Louis-Nicolas Vauquelin and Pierre Jean Robiquet isolated a compound in asparagus that proved to be asparagine, the first amino



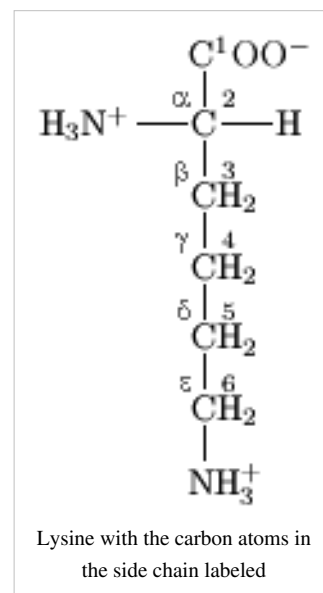
The twenty-one amino acids found in eukaryotes, grouped according to their side chains' pKa's and charge at physiological pH 7.4

acid to be discovered.^{[3] [4]} Another amino acid that was discovered in the early 19th century was cystine, in 1810,^[5] although its monomer, cysteine, was discovered much later, in 1884.^{[4] [6]} Glycine and leucine were also discovered around this time, in 1820.^[7] Usage of the term *amino acid* in the English language is from 1898.^[8]

General structure

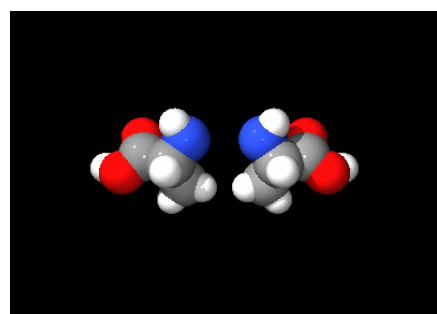
In the structure shown at the top of the page, **R** represents a side chain specific to each amino acid. The carbon atom next to the carboxyl group is called the α -carbon and amino acids with a side chain bonded to this carbon are referred to as *alpha amino acids*. These are the most common form found in nature. In the alpha amino acids, the α -carbon is a chiral carbon atom, with the exception of glycine.^[9] In amino acids that have a carbon chain attached to the α -carbon (such as lysine, shown to the right) the carbons are labeled in order as α , β , γ , δ , and so on.^[10] In some amino acids, the amine group is attached to the β or γ -carbon, and these are therefore referred to as *beta* or *gamma amino acids*.

Amino acids are usually classified by the properties of their side chain into four groups. The side chain can make an amino acid a weak acid or a weak base, and a hydrophile if the side chain is polar or a hydrophobe if it is nonpolar.^[9] The chemical structures of the twenty-two standard amino acids, along with their chemical properties, are described more fully in the article on these proteinogenic amino acids.



Lysine with the carbon atoms in the side chain labeled

The phrase "branched-chain amino acids" or BCAA refers to the amino acids having aliphatic side chains that are non-linear; these are leucine, isoleucine, and valine. Proline is the only proteinogenic amino acid whose side group links to the α -amino group and, thus, is also the only proteinogenic amino acid containing a secondary amine at this position.^[9] Chemically, proline is therefore an imino acid since it lacks a primary amino group,^[11] although it is still classed as an amino acid in the current biochemical nomenclature,^[12] and may also be called an "N-alkylated alpha-amino acid".^[13]



The two optical isomers of alanine, D-Alanine and L-Alanine

Isomerism

Of the standard α -amino acids, all but glycine can exist in either of two optical isomers, called L or D amino acids, which are mirror images of each other (*see also Chirality*). While L-amino acids represent all of the amino acids found in proteins during translation in the ribosome, D-amino acids are found in some proteins produced by enzyme posttranslational modifications after translation and translocation to the endoplasmic reticulum, as in exotic sea-dwelling organisms such as cone snails.^[14] They are also abundant components of the peptidoglycan cell walls of bacteria,^[15] and D-serine may act as a neurotransmitter in the brain.^[16] The L and D convention for amino

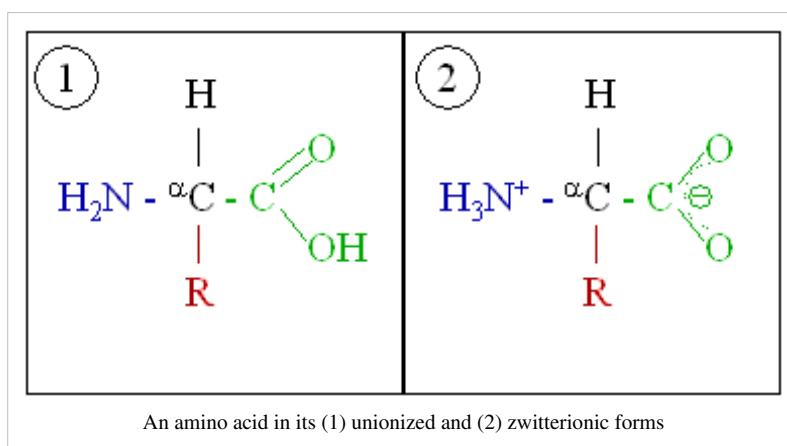
acid configuration refers not to the optical activity of the amino acid itself, but rather to the optical activity of the isomer of glyceraldehyde from which that amino acid can theoretically be synthesized (D-glyceraldehyde is dextrorotary; L-glyceraldehyde is levorotary). Alternatively, the (*S*) and (*R*) designators are used to indicate the absolute stereochemistry. Almost all of the amino acids in proteins are (*S*) at the α carbon, with cysteine being (*R*) and glycine non-chiral.^[17] Cysteine is unusual since it has a sulfur atom at the second position in its side-chain, which has a larger atomic mass than the groups attached to the first carbon which is attached to the α -carbon in the other standard amino acids, thus the (*R*) instead of (*S*).

Zwitterions

The amine and carboxylic acid functional groups found in amino acids allow it to have amphiprotic properties.^[9] At a certain pH, known as the isoelectric point, an amino acid has no overall charge since the number of protonated ammonia groups (positive charges) and deprotonated carboxylate groups (negative charges) are equal.^[18]

The amino acids all have different

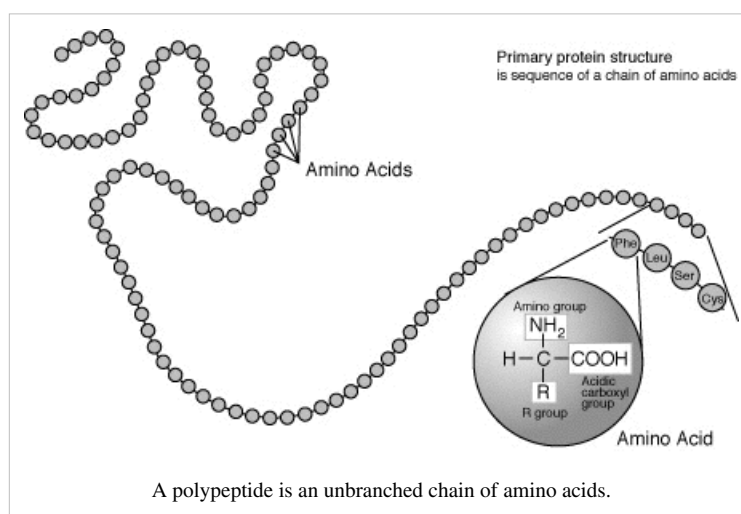
isoelectric points. The ions produced at the isoelectric point have both positive and negative charges and are known as a *zwitterion*, which comes from the German word *Zwitter* meaning "hermaphrodite" or "hybrid".^[19] Amino acids can exist as zwitterions in solids and in polar solutions such as water, but not in the gas phase.^[20] Zwitterions have minimal solubility at their isoelectric point and an amino acid can be isolated by precipitating it from water by adjusting the pH to its particular isoelectric point.



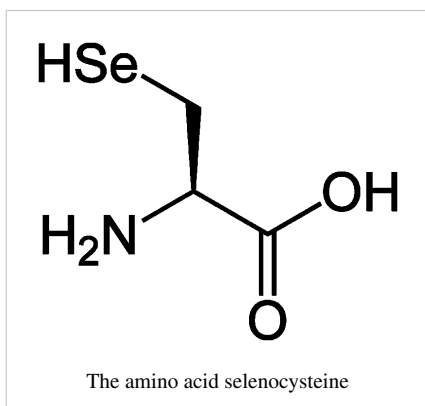
Occurrence and functions in biochemistry

Standard amino acids

Amino acids are the structural units that make up proteins. They join together to form short polymer chains called peptides or longer chains called either polypeptides or proteins. These polymers are linear and unbranched, with each amino acid within the chain attached to two neighboring amino acids. The process of making proteins is called *translation* and involves the step-by-step addition of amino acids to a growing protein chain by a ribozyme that is called a ribosome.^[21] The order in which the amino acids are added is read through the genetic code from an mRNA template, which is a RNA copy of one of the organism's genes.



Twenty-two amino acids are naturally incorporated into polypeptides and are called proteinogenic or standard amino acids.^[9] Of these twenty-two, twenty are encoded by the universal genetic code. The remaining two, selenocysteine and pyrrolysine, are incorporated into proteins by unique synthetic mechanisms. Selenocysteine is incorporated when the mRNA being translated includes a SECIS element, which causes the UGA codon to encode selenocysteine instead of a stop codon.^[22] Pyrrolysine is used by some methanogenic archaea in enzymes that they use to produce methane. It is coded for with the codon UAG, which is normally a stop codon in other organisms.^[23]

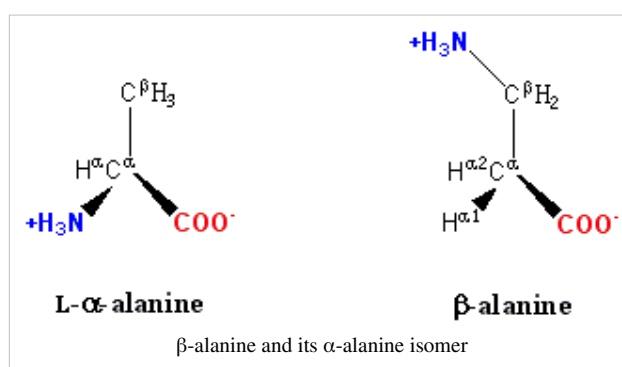


Non-standard amino acids

Aside from the twenty-two standard amino acids, there are a vast number of "non-standard" amino acids. These non-standard amino acids found in proteins are formed by post-translational modification, which is modification after translation in protein synthesis. These modifications are often essential for the function or regulation of a protein; for example, the carboxylation of glutamate allows for better binding of calcium cations,^[24] and the hydroxylation of proline is critical for maintaining connective tissues.^[25] Another example is the formation of hypusine in the translation initiation factor EIF5A, through modification of a lysine residue.^[26] Such modifications can also determine the localization of the

protein, e.g., the addition of long hydrophobic groups can cause a protein to bind to a phospholipid membrane.^[27]

Examples of nonstandard amino acids that are not found in proteins include lanthionine, 2-aminoisobutyric acid, dehydroalanine and the neurotransmitter gamma-aminobutyric acid. Nonstandard amino acids often occur as intermediates in the metabolic pathways for standard amino acids — for example ornithine and citrulline occur in the urea cycle, part of amino acid catabolism (see below).^[28] A rare exception to the dominance of α -amino acids in biology is the β -amino acid beta alanine (3-aminopropanoic acid), which is used in plants and microorganisms in the synthesis of pantothenic acid (vitamin B₅), a component of coenzyme A.^[29]



In human nutrition

When taken up into the human body from the diet, the twenty-two standard amino acids are either used to synthesize proteins and other biomolecules or oxidized to urea and carbon dioxide as a source of energy.^[30] The oxidation pathway starts with the removal of the amino group by a transaminase, the amino group is then fed into the urea cycle. The other product of transamidation is a keto acid that enters the citric acid cycle.^[31] Glucogenic amino acids can also be converted into glucose, through gluconeogenesis.^[32]

Pyrrolysine trait is restricted to several microbes, and only one organism has both Pyl and Sec. Of the twenty-two standard amino acids, eight are called essential amino acids because the human body cannot synthesize them from other compounds at the level needed for normal growth, so they must be obtained from food.^[33] However, the situation is quite complicated since cysteine, taurine, tyrosine, histidine and arginine are semiessential amino acids in children, because the metabolic pathways that synthesize these amino acids are not fully developed.^[34] ^[35] The amounts required also depend on the age and health of the individual, so it is hard to make general statements about the dietary requirement for some amino acids.

Essential	Nonessential
Isoleucine	Alanine
Leucine	Asparagine
Lysine	Aspartic Acid
Methionine	Cysteine*
Phenylalanine	Glutamic Acid
Threonine	Glutamine*
Tryptophan	Glycine*
Valine	Proline*
	Selenocysteine*
	Serine*
	Tyrosine*
	Arginine*
	Histidine*
	Ornithine*
	Taurine*

(*) Essential only in certain cases.^{[36] [37]}

Non-protein functions

In humans, non-protein amino acids also have important roles as metabolic intermediates, such as in the biosynthesis of the neurotransmitter gamma-aminobutyric acid. Many amino acids are used to synthesize other molecules, for example:

- Tryptophan is a precursor of the neurotransmitter serotonin.^[38]
- Tyrosine is a precursor of the neurotransmitter dopamine.
- Glycine is a precursor of porphyrins such as heme.^[39]
- Arginine is a precursor of nitric oxide.^[40]
- Ornithine and S-adenosylmethionine are precursors of polyamines.^[41]
- Aspartate, glycine and glutamine are precursors of nucleotides.^[42]
- Phenylalanine is a precursor of various phenylpropanoids which are important in plant metabolism.

However, not all of the functions of other abundant non-standard amino acids are known, for example taurine is a major amino acid in muscle and brain tissues, but although many functions have been proposed, its precise role in the body has not been determined.^[43]

Some non-standard amino acids are used as defenses against herbivores in plants.^[44] For example canavanine is an analogue of arginine that is found in many legumes,^[45] and in particularly large amounts in *Canavalia gladiata* (sword bean).^[46] This amino acid protects the plants from predators such as insects and can cause illness in people if some types of legumes are eaten without processing.^[47] The non-protein amino acid mimosine is found in other species of legume, particularly *Leucaena leucocephala*.^[48] This compound is an analogue of tyrosine and can poison animals that graze on these plants.

Uses in technology

Amino acids are used for a variety of applications in industry but their main use is as additives to animal feed. This is necessary since many of the bulk components of these feeds, such as soybeans, either have low levels or lack some of the essential amino acids: lysine, methionine, threonine, and tryptophan are most important in the production of these feeds.^[49] The food industry is also a major consumer of amino acids, particularly glutamic acid, which is used as a flavor enhancer,^[50] and Aspartame (aspartyl-phenylalanine-1-methyl ester) as a low-calorie artificial sweetener.^[51] The remaining production of amino acids is used in the synthesis of drugs and cosmetics.^[49]

Amino acid derivative	Pharmaceutical application
5-HTP (5-hydroxytryptophan)	Experimental treatment for depression. ^[52]
L-DOPA (L-dihydroxyphenylalanine)	Treatment for Parkinsonism. ^[53]
Eflornithine	Drug that inhibits ornithine decarboxylase and is used in the treatment of sleeping sickness. ^[54]

Expanded genetic code

Since 2001, 40 non-natural amino acids have been added into protein by creating a unique codon (recoding) and a corresponding transfer-RNA:aminoacyl – tRNA-synthetase pair to encode it with diverse physicochemical and biological properties in order to be used as a tool to exploring protein structure and function or to create novel or enhanced proteins.^{[55] [56]}

Chemical building blocks

Amino acids are important as low-cost feedstocks. These compounds are used in chiral pool synthesis as enantiomerically-pure building blocks.^[57]

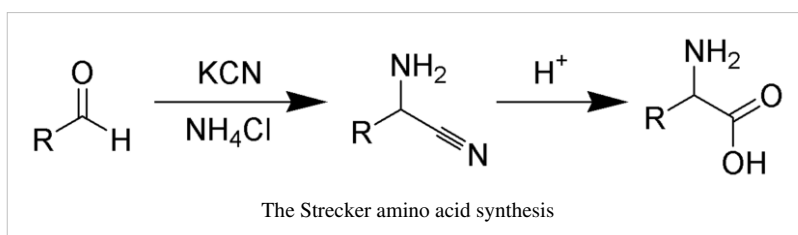
Amino acids have been investigated as precursors chiral catalysts, e.g. for asymmetric hydrogenation reactions, although no commercial applications exist.^[58]

Biodegradable plastics

Amino acids are under development as components of a range of biodegradable polymers. These materials have applications as environmentally-friendly packaging and in medicine in drug delivery and the construction of prosthetic implants. These polymers include polypeptides, polyamides, polyesters, polysulfides and polyurethanes with amino acids either forming part of their main chains or bonded as side chains. These modifications alter the physical properties and reactivities of the polymers.^[59] An interesting example of such materials is polyaspartate, a water-soluble biodegradable polymer that may have applications in disposable diapers and agriculture.^[60] Due to its solubility and ability to chelate metal ions, polyaspartate is also being used as a biodegradeable anti-scaling agent and a corrosion inhibitor.^{[61] [62]} In addition, the aromatic amino acid tyrosine is being developed as a possible replacement for toxic phenols such as bisphenol A in the manufacture of polycarbonates.^[63]

Reactions

As amino acids have both a primary amine group and a primary carboxyl group, these chemicals can undergo most of the reactions associated with these functional groups. These include nucleophilic addition, amide bond formation and imine formation for the amine group and esterification, amide bond formation and decarboxylation for the carboxylic acid group.^[64] The multiple side chains of amino acids can also undergo chemical reactions.^[65] The types of these reactions are determined by the groups on these side chains and are therefore different between the various types of amino acid.



Chemical synthesis

Several methods exist to synthesize amino acids. One of the oldest methods, begins with the bromination at the α -carbon of a carboxylic acid.

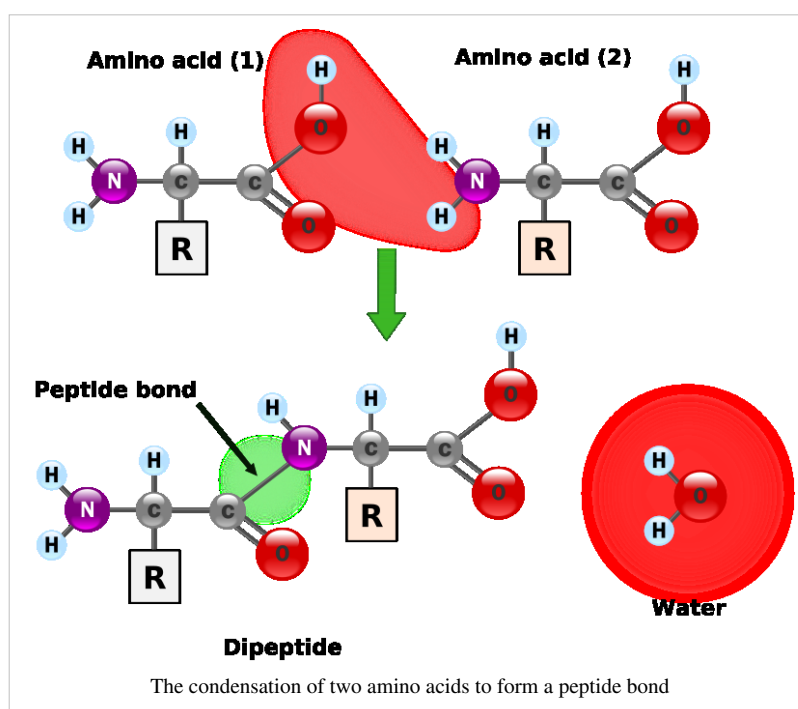
Nucleophilic substitution with

ammonia then converts the alkyl bromide to the amino acid.^[66] Alternatively, the Strecker amino acid synthesis involves the treatment of an aldehyde with potassium cyanide and ammonia, this produces an α -amino nitrile as an intermediate. Hydrolysis of the nitrile in acid then yields a α -amino acid.^[67] Using ammonia or ammonium salts in this reaction gives unsubstituted amino acids, while substituting primary and secondary amines will yield substituted amino acids.^[68] Likewise, using ketones, instead of aldehydes, gives α,α -disubstituted amino acids.^[69] The classical synthesis gives racemic mixtures of α -amino acids as products, but several alternative procedures using asymmetric auxiliaries^[70] or asymmetric catalysts^{[71] [72]} have been developed.^[73]

Currently the most adopted method is an automated synthesis on a solid support (e.g. polystyrene beads), using protecting groups (e.g. Fmoc and t-Boc) and activating groups (e.g. DCC and DIC).

Peptide bond formation

As both the amine and carboxylic acid groups of amino acids can react to form amide bonds, one amino acid molecule can react with another and become joined through an amide linkage. This polymerization of amino acids is what creates proteins. This condensation reaction yields the newly formed peptide bond and a molecule of water. In cells, this reaction does not occur directly; instead the amino acid is first activated by attachment to a transfer RNA molecule through an ester bond. This aminoacyl-tRNA is produced in an ATP-dependent reaction carried out by an aminoacyl tRNA synthetase.^[74] This aminoacyl-tRNA is then a substrate for the ribosome, which catalyzes the



attack of the amino group of the elongating protein chain on the ester bond.^[75] As a result of this mechanism, all proteins made by ribosomes are synthesized starting at their N-terminus and moving towards their C-terminus.

However, not all peptide bonds are formed in this way. In a few cases, peptides are synthesized by specific enzymes. For example, the tripeptide glutathione is an essential part of the defenses of cells against oxidative stress. This peptide is synthesized in two steps from free amino acids.^[76] In the first step gamma-glutamylcysteine synthetase condenses cysteine and glutamic acid through a peptide bond formed between the side-chain carboxyl of the glutamate (the gamma carbon of this side chain) and the amino group of the cysteine. This dipeptide is then condensed with glycine by glutathione synthetase to form glutathione.^[77]

In chemistry, peptides are synthesized by a variety of reactions. One of the most used in solid-phase peptide synthesis, which uses the aromatic oxime derivatives of amino acids as activated units. These are added in sequence onto the growing peptide chain, which is attached to a solid resin support.^[78] The ability to easily synthesize vast numbers of different peptides by varying the types and order of amino acids (using combinatorial chemistry) has made peptide synthesis particularly important in creating libraries of peptides for use in drug discovery through high-throughput screening.^[79]

Biosynthesis and catabolism

In plants, nitrogen is first assimilated into organic compounds in the form of glutamate, formed from alpha-ketoglutarate and ammonia in the mitochondrion. In order to form other amino acids, the plant uses transaminases to move the amino group to another alpha-keto carboxylic acid. For example, aspartate aminotransferase converts glutamate and oxaloacetate to alpha-ketoglutarate and aspartate.^[80] Other organisms use transaminases for amino acid synthesis too. Transaminases are also involved in breaking down amino acids. Degrading an amino acid often involves moving its amino group to alpha-ketoglutarate, forming glutamate. In many vertebrates, the amino group is then removed through the urea cycle and is excreted in the form of urea. However, amino acid degradation can produce uric acid or ammonia instead. For example, serine dehydratase converts serine to pyruvate and ammonia.^[81]

Nonstandard amino acids are usually formed through modifications to standard amino acids. For example, homocysteine is formed through the transsulfuration pathway or by the demethylation of methionine via the intermediate metabolite S-adenosyl methionine,^[43] while hydroxyproline is made by a posttranslational modification of proline.^[82]

Microorganisms and plants can synthesize many uncommon amino acids. For example, some microbes make 2-aminoisobutyric acid and lanthionine, which is a sulfide-bridged derivative of alanine. Both of these amino acids are found in peptidic lantibiotics such as alamethicin.^[83] While in plants, 1-aminocyclopropane-1-carboxylic acid is a small disubstituted cyclic amino acid that is a key intermediate in the production of the plant hormone ethylene.^[84]

Physicochemical properties of amino acids

The 20 amino acids encoded directly by the genetic code can be divided into several groups based on their properties. Important factors are charge, hydrophilicity or hydrophobicity, size and functional groups.^[9] These properties are important for protein structure and protein–protein interactions. The water-soluble proteins tend to have their hydrophobic residues (Leu, Ile, Val, Phe and Trp) buried in the middle of the protein, whereas hydrophilic side chains are exposed to the aqueous solvent. The integral membrane proteins tend to have outer rings of exposed hydrophobic amino acids that anchor them into the lipid bilayer. In the case part-way between these two extremes, some peripheral membrane proteins have a patch of hydrophobic amino acids on their surface that locks onto the membrane. Similarly, proteins that have to bind to positively-charged molecules have surfaces rich with negatively charged amino acids like glutamate and aspartate, while proteins binding to negatively-charged molecules have surfaces rich with positively charged chains like lysine and arginine. There are different hydrophobicity scales of amino acid residues.^[85]

Some amino acids have special properties such as cysteine, that can form covalent disulfide bonds to other cysteine residues, proline that forms a cycle to the polypeptide backbone, and glycine that is more flexible than other amino acids.

Many proteins undergo a range of posttranslational modifications, when additional chemical groups are attached to the amino acids in proteins. Some modifications can produce hydrophobic lipoproteins,^[86] or hydrophilic glycoproteins.^[87] These type of modification allow the reversible targeting of a protein to a membrane. For example, the addition and removal of the fatty acid palmitic acid to cysteine residues in some signaling proteins causes the proteins to attach and then detach from cell membranes.^[88]

Table of standard amino acid abbreviations and properties

Amino Acid	3-Letter ^[89]	1-Letter ^[89]	Side chain polarity ^[89]	Side chain charge (pH 7.4) ^[89]	Hydropathy index ^[90]	Absorbance λ_{max} (nm) ^[91]	ϵ at λ_{max} ($\times 10^{-3}$ M ⁻¹ cm ⁻¹) ^[91]
Alanine	Ala	A	nonpolar	neutral	1.8		
Arginine	Arg	R	polar	positive	-4.5		
Asparagine	Asn	N	polar	neutral	-3.5		
Aspartic acid	Asp	D	polar	negative	-3.5		
Cysteine	Cys	C	nonpolar	neutral	2.5	250	0.3
Glutamic acid	Glu	E	polar	negative	-3.5		
Glutamine	Gln	Q	polar	neutral	-3.5		
Glycine	Gly	G	nonpolar	neutral	-0.4		
Histidine	His	H	polar	positive(10%) neutral(90%)	-3.2	211	5.9
Isoleucine	Ile	I	nonpolar	neutral	4.5		
Leucine	Leu	L	nonpolar	neutral	3.8		
Lysine	Lys	K	polar	positive	-3.9		
Methionine	Met	M	nonpolar	neutral	1.9		
Phenylalanine	Phe	F	nonpolar	neutral	2.8	257, 206, 188	0.2, 9.3, 60.0
Proline	Pro	P	nonpolar	neutral	-1.6		
Serine	Ser	S	polar	neutral	-0.8		
Threonine	Thr	T	polar	neutral	-0.7		
Tryptophan	Trp	W	nonpolar	neutral	-0.9	280, 219	5.6, 47.0
Tyrosine	Tyr	Y	polar	neutral	-1.3	274, 222, 193	1.4, 8.0, 48.0
Valine	Val	V	nonpolar	neutral	4.2		

Additionally, there are two additional amino acids which are incorporated by overriding stop codons:

21st and 22nd amino acids	3-Letter	1-Letter
Selenocysteine	Sec	U
Pyrrolysine	Pyl	O

In addition to the specific amino acid codes, placeholders are used in cases where chemical or crystallographic analysis of a peptide or protein can not conclusively determine the identity of a residue.

Ambiguous Amino Acids	3-Letter	1-Letter
Asparagine or aspartic acid	Asx	B
Glutamine or glutamic acid	Glx	Z
Leucine or Isoleucine	Xle	J
Unspecified or unknown amino acid	Xaa	X

Unk is sometimes used instead of **Xaa**, but is less standard.

Additionally, many non-standard amino acids have a specific code. For example, several peptide drugs, such as Bortezomib or MG132 are artificially synthesized and retain their protecting groups, which have specific codes. Bortezomib is Pyz-Phe-boroLeu and MG132 is Z-Leu-Leu-Leu-al. Additionally, To aid in the analysis of protein structure, photocrosslinking amino acid analogues are available. These include photoleucine (**pLeu**) and photomethionine (**pMet**).^[92]

References and notes

- [1] Proline is an exception to this general formula. It lacks the NH_2 group because of the cyclization of the side chain and is known as an imino acid; it falls under the category of special structured amino acids.
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External links

- Amino acids overview (<http://www.peptideguide.com/amino-acids/index.html>) physical-chemistry properties, 3D structures, etc.
- List of Standard Amino Acids (<http://www.unc.edu/~bzafer/aminoacids/>) The Detailed PDF List of Standard Amino Acids (including 3D depictions)
- Nomenclature and Symbolism for Amino Acids and Peptides (<http://www.chem.qmul.ac.uk/iupac/AminoAcid/>) IUPAC-IUB Joint Commission on Biochemical Nomenclature (JCBN)
- Molecular Expressions: The Amino Acid Collection (<http://micro.magnet.fsu.edu/aminoacids/index.html>) – Has detailed information and microscopy photographs of each amino acid.
- Amino acid properties (<http://www.russell.embl.de/aas/>) – Properties of the amino acids (a tool aimed mostly at molecular geneticists trying to understand the meaning of mutations)

- Synthesis of Amino Acids and Derivatives (<http://www.organic-chemistry.org/synthesis/C1C/nitrogen/alpha-amino-acids2.shtm>)
- Learn the 20 proteinogenic amino acids online (<http://www.mathiasbader.de/studium/biology/index.php?lng=en>)
- The origin of the single-letter code for the amino acids (http://www.biology.arizona.edu/biochemistry/problem_sets/aa/Dayhoff.html)
- Amino acid solution's pH, titration and isoelectric point calculation free spreadsheet (http://www2.iq.usp.br/docente/gutz/Curtpot_.html)

Proteins

Proteins (also known as **polypeptides**) are organic compounds made of amino acids arranged in a linear chain and folded into a globular form. The amino acids in a polymer are joined together by the peptide bonds between the carboxyl and amino groups of adjacent amino acid residues. The sequence of amino acids in a protein is defined by the sequence of a gene, which is encoded in the genetic code.^[1] In general, the genetic code specifies 20 standard amino acids; however, in certain organisms the genetic code can include selenocysteine—and in certain archaea—pyrrolysine. Shortly after or even during synthesis, the residues in a protein are often chemically modified by post-translational modification, which alters the physical and chemical properties, folding, stability, activity, and ultimately, the function of the proteins. Proteins can also work together to achieve a particular function, and they often associate to form stable complexes.^[2]

Of the most distinguishing features of polypeptides is their ability to fold into a globular state, or "structure". The extent to which proteins fold into a defined structure varies widely. Data supports that some protein structures fold into a highly rigid structure with small fluctuations and are therefore considered to be single structure. Other proteins have been shown to undergo large rearrangements from one conformation to another. This conformational change is often associated with a signaling event. Thus, the structure of a protein serves as a medium through which to regulate either the function of a protein or activity of an enzyme. Not all proteins requiring a folding process in order to function as some function in an unfolded state.

Like other biological macromolecules such as polysaccharides and nucleic acids, proteins are essential parts of organisms and participate in virtually every process within cells. Many proteins are enzymes that catalyze biochemical reactions and are vital to metabolism. Proteins also have structural or mechanical functions, such as actin and myosin in muscle and the proteins in the cytoskeleton, which form a system of scaffolding that maintains cell shape. Other proteins are important in cell signaling, immune responses, cell adhesion, and the cell cycle. Proteins are also necessary in animals' diets, since animals cannot synthesize all the amino acids they need and must obtain essential amino acids from food. Through the process of digestion, animals break down ingested protein into free amino acids that are then used in metabolism.

Proteins were first described by the Dutch chemist Gerhardus Johannes Mulder and named by the Swedish chemist Jöns Jakob Berzelius in 1838. Early nutritional scientists such as the German Carl von Voit believed that protein was the most important nutrient for maintaining the structure of the body, because it was generally believed that "flesh makes flesh."^[3] The central role of proteins as enzymes in living organisms was however not fully appreciated until 1926, when James B. Sumner showed that the enzyme urease was in fact a protein.^[4] The first protein to be sequenced was insulin, by Frederick Sanger, who won the Nobel Prize for this achievement in 1958. The first protein structures to be solved were hemoglobin and myoglobin, by Max Perutz and Sir John Cowdery Kendrew, respectively, in 1958.^[5] ^[6] The three-dimensional structures of both proteins were first determined by x-ray diffraction analysis; Perutz and Kendrew shared the 1962 Nobel Prize in Chemistry for these discoveries. Proteins may be purified from other cellular components using a variety of techniques such as ultracentrifugation, precipitation, electrophoresis, and chromatography; the advent of genetic engineering has made possible a number of

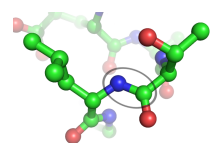
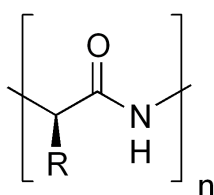
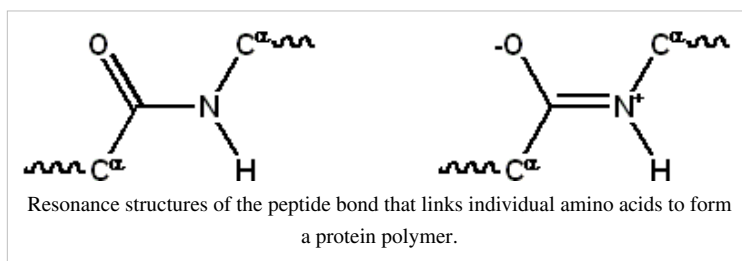
methods to facilitate purification. Methods commonly used to study protein structure and function include immunohistochemistry, site-directed mutagenesis, nuclear magnetic resonance and mass spectrometry.

Biochemistry

Most proteins are linear polymers built from series of up to 20 different L- α -amino acids. All amino acids possess common structural features, including an α -carbon to which an amino group, a carboxyl group, and a variable side chain are bonded. Only proline differs from this basic structure as it contains an unusual ring to the N-end amine group, which forces the CO–NH amide moiety into a fixed conformation.^[7] The side chains of the standard amino acids, detailed in the list of standard amino acids, have a great variety of chemical structures and properties; it is the combined effect of all of the amino acid side chains in a protein that ultimately determines its three-dimensional structure and its chemical reactivity.^[8]



A representation of the 3D structure of myoglobin showing coloured alpha helices. This protein was the first to have its structure solved by X-ray crystallography.



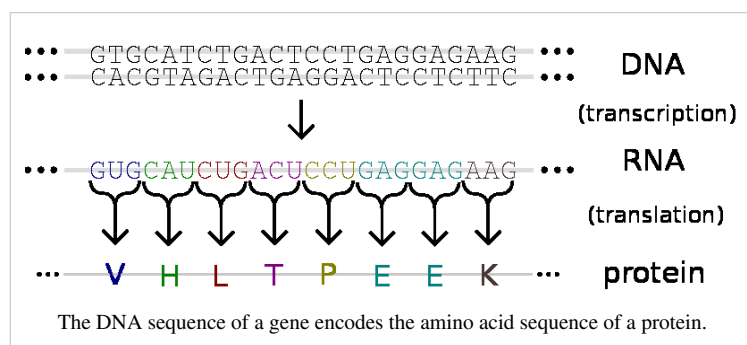
Chemical structure of the peptide bond (left) and a peptide bond between leucine and threonine (right).

The amino acids in a polypeptide chain are linked by peptide bonds. Once linked in the protein chain, an individual amino acid is called a *residue*, and the linked series of carbon, nitrogen, and oxygen atoms are known as the *main chain* or *protein backbone*.^[9] The peptide bond has two resonance forms that contribute some double-bond character and inhibit rotation around its axis, so that the alpha carbons are roughly coplanar. The other two dihedral angles in the peptide bond determine the local shape assumed by the protein backbone.^[10] The end of the protein with a free carboxyl group is known as the C-terminus or carboxy terminus, whereas the end with a free amino group is known as the N-terminus or amino terminus.

The words *protein*, *polypeptide*, and *peptide* are a little ambiguous and can overlap in meaning. *Protein* is generally used to refer to the complete biological molecule in a stable conformation, whereas *peptide* is generally reserved for a short amino acid oligomers often lacking a stable three-dimensional structure. However, the boundary between the

two is not well defined and usually lies near 20–30 residues.^[11] *Polypeptide* can refer to any single linear chain of amino acids, usually regardless of length, but often implies an absence of a defined conformation.

Synthesis



Proteins are assembled from amino acids using information encoded in genes. Each protein has its own unique amino acid sequence that is specified by the nucleotide sequence of the gene encoding this protein. The genetic code is a set of three-nucleotide sets called codons and each three-nucleotide combination designates an amino acid, for example AUG (adenine-uracil-guanine) is the code for methionine. Because DNA

contains four nucleotides, the total number of possible codons is 64; hence, there is some redundancy in the genetic code, with some amino acids specified by more than one codon.^[12] Genes encoded in DNA are first transcribed into pre-messenger RNA (mRNA) by proteins such as RNA polymerase. Most organisms then process the pre-mRNA (also known as a *primary transcript*) using various forms of post-transcriptional modification to form the mature mRNA, which is then used as a template for protein synthesis by the ribosome. In prokaryotes the mRNA may either be used as soon as it is produced, or be bound by a ribosome after having moved away from the nucleoid. In contrast, eukaryotes make mRNA in the cell nucleus and then translocate it across the nuclear membrane into the cytoplasm, where protein synthesis then takes place. The rate of protein synthesis is higher in prokaryotes than eukaryotes and can reach up to 20 amino acids per second.^[13]

The process of synthesizing a protein from an mRNA template is known as translation. The mRNA is loaded onto the ribosome and is read three nucleotides at a time by matching each codon to its base pairing anticodon located on a transfer RNA molecule, which carries the amino acid corresponding to the codon it recognizes. The enzyme aminoacyl tRNA synthetase "charges" the tRNA molecules with the correct amino acids. The growing polypeptide is often termed the *nascent chain*. Proteins are always biosynthesized from N-terminus to C-terminus.^[12]

The size of a synthesized protein can be measured by the number of amino acids it contains and by its total molecular mass, which is normally reported in units of *daltons* (synonymous with atomic mass units), or the derivative unit kilodalton (kDa). Yeast proteins are on average 466 amino acids long and 53 kDa in mass.^[11] The largest known proteins are the titins, a component of the muscle sarcomere, with a molecular mass of almost 3,000 kDa and a total length of almost 27,000 amino acids.^[14]

Chemical synthesis

Short proteins can also be synthesized chemically by a family of methods known as peptide synthesis, which rely on organic synthesis techniques such as chemical ligation to produce peptides in high yield.^[15] Chemical synthesis allows for the introduction of non-natural amino acids into polypeptide chains, such as attachment of fluorescent probes to amino acid side chains.^[16] These methods are useful in laboratory biochemistry and cell biology, though generally not for commercial applications. Chemical synthesis is inefficient for polypeptides longer than about 300 amino acids, and the synthesized proteins may not readily assume their native tertiary structure. Most chemical synthesis methods proceed from C-terminus to N-terminus, opposite the biological reaction.^[17]

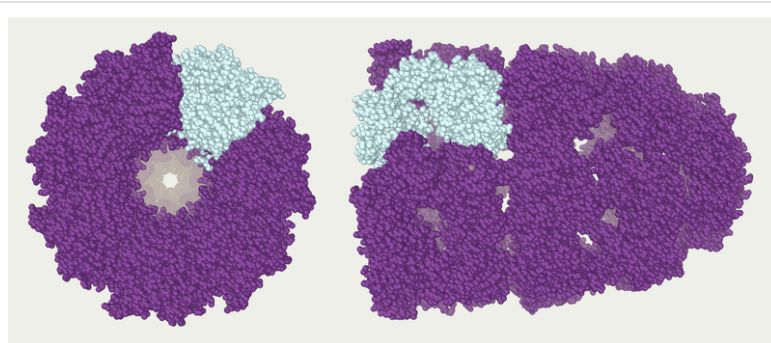
Structure

Most proteins fold into unique 3-dimensional structures. The shape into which a protein naturally folds is known as its native conformation.^[18]

Although many proteins can fold unassisted, simply through the chemical properties of their amino acids, others require the aid of molecular chaperones to fold into their native states.^[19] Biochemists often refer to four distinct aspects of a protein's structure:^[20]

- *Primary structure*: the amino acid sequence.
- *Secondary structure*: regularly repeating local structures stabilized by hydrogen bonds. The most common examples are the alpha helix, beta sheet and turns. Because secondary structures are local, many regions of different secondary structure can be present in the same protein molecule.
- *Tertiary structure*: the overall shape of a single protein molecule; the spatial relationship of the secondary structures to one another. Tertiary structure is generally stabilized by nonlocal interactions, most commonly the formation of a hydrophobic core, but also through salt bridges, hydrogen bonds, disulfide bonds, and even post-translational modifications. The term "tertiary structure" is often used as synonymous with the term *fold*. The tertiary structure is what controls the basic function of the protein.
- *Quaternary structure*: the structure formed by several protein molecules (polypeptide chains), usually called *protein subunits* in this context, which function as a single protein complex.

Proteins are not entirely rigid molecules. In addition to these levels of structure, proteins may shift between several related structures while they perform their functions. In the context of these functional rearrangements, these tertiary or quaternary structures are usually referred to as "conformations", and transitions between them are called *conformational changes*. Such changes are often induced by the binding of a substrate molecule to an enzyme's active site, or the physical region of the protein that participates in chemical catalysis. In solution proteins also undergo variation in structure through thermal vibration and the collision with other molecules.^[21]

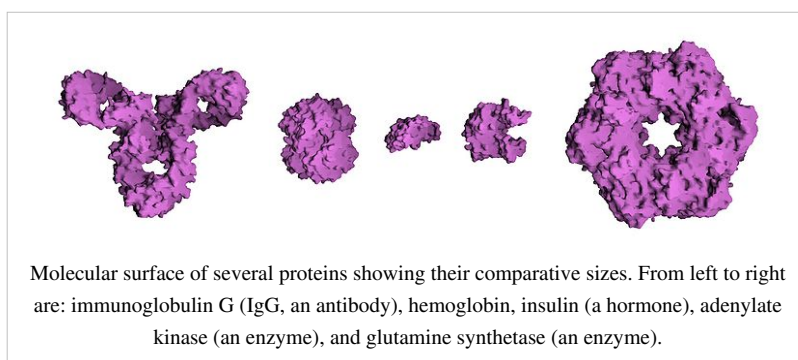


The crystal structure of the chaperonin. Chaperonins assist protein folding.



Three possible representations of the three-dimensional structure of the protein triose phosphate isomerase. Left: all-atom representation colored by atom type. Middle: Simplified representation illustrating the backbone conformation, colored by secondary structure. Right: Solvent-accessible surface representation colored by residue type (acidic residues red, basic residues blue, polar residues green, nonpolar residues white).

Proteins can be informally divided into three main classes, which correlate with typical tertiary structures: globular proteins, fibrous proteins, and membrane proteins. Almost all globular proteins are soluble and many are enzymes. Fibrous proteins are often structural, such as collagen, the major component of connective tissue, or keratin, the protein component of hair and nails. Membrane proteins often serve as receptors or provide channels for polar or charged molecules to pass through the cell membrane.^[22]



A special case of intramolecular hydrogen bonds within proteins, poorly shielded from water attack and hence promoting their own dehydration, are called dehydrons.^[23]

Structure determination

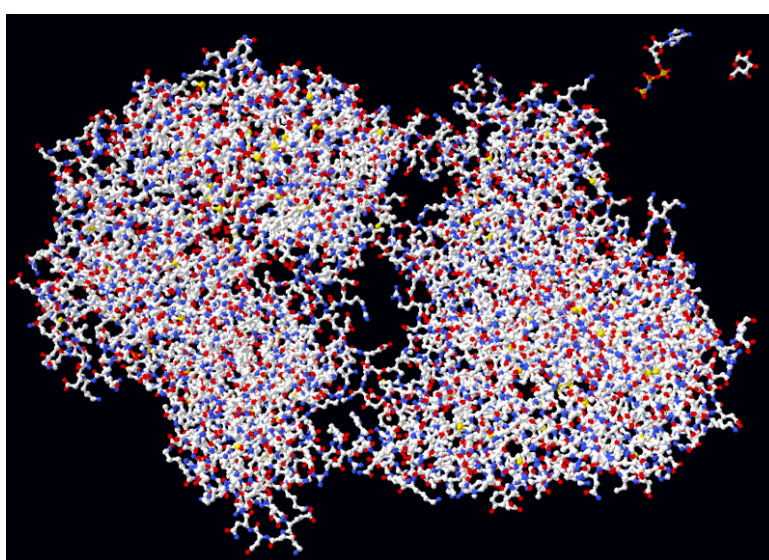
Discovering the tertiary structure of a protein, or the quaternary structure of its complexes, can provide important clues about how the protein performs its function. Common experimental methods of structure determination include X-ray crystallography and NMR spectroscopy, both of which can produce information at atomic resolution. However, NMR experiments are able to provide information from which a subset of distances between pairs of atoms can be estimated, and the final possible conformations for a protein are determined by solving a distance geometry problem. Dual polarisation interferometry is a quantitative analytical method for measuring the overall protein conformation and conformational changes due to interactions or other stimulus. Circular dichroism is another laboratory technique for determining internal beta sheet/ helical composition of proteins. Cryoelectron microscopy is used to produce lower-resolution structural information about very large protein complexes, including assembled viruses;^[24] a variant known as electron crystallography can also produce high-resolution information in some cases, especially for two-dimensional crystals of membrane proteins.^[25] Solved structures are usually deposited in the Protein Data Bank (PDB), a freely available resource from which structural data about thousands of proteins can be obtained in the form of Cartesian coordinates for each atom in the protein.^[26]

Many more gene sequences are known than protein structures. Further, the set of solved structures is biased toward proteins that can be easily subjected to the conditions required in X-ray crystallography, one of the major structure determination methods. In particular, globular proteins are comparatively easy to crystallize in preparation for X-ray crystallography. Membrane proteins, by contrast, are difficult to crystallize and are underrepresented in the PDB.^[27] Structural genomics initiatives have attempted to remedy these deficiencies by systematically solving representative structures of major fold classes. Protein structure prediction methods attempt to provide a means of generating a plausible structure for proteins whose structures have not been experimentally determined.

Cellular functions

Proteins are the chief actors within the cell, said to be carrying out the duties specified by the information encoded in genes.^[11] With the exception of certain types of RNA, most other biological molecules are relatively inert elements upon which proteins act. Proteins make up half the dry weight of an *Escherichia coli* cell, whereas other macromolecules such as DNA and RNA make up only 3% and 20%, respectively.^[28] The set of proteins expressed in a particular cell or cell type is known as its proteome.

The chief characteristic of proteins that also allows their diverse set of functions is their ability to bind other molecules specifically and tightly. The region of the protein responsible for binding another molecule is known as the binding site and is often a depression or "pocket" on the molecular surface. This binding ability is mediated by the tertiary structure of the protein, which defines the binding site pocket, and by the chemical properties of the surrounding amino acids' side chains. Protein binding can be extraordinarily tight and specific; for example, the ribonuclease inhibitor protein binds to human angiogenin



The enzyme hexokinase is shown as a simple ball-and-stick molecular model. To scale in the top right-hand corner are two of its substrates, ATP and glucose.

with a sub-femtomolar dissociation constant ($<10^{-15}$ M) but does not bind at all to its amphibian homolog onconase (>1 M). Extremely minor chemical changes such as the addition of a single methyl group to a binding partner can sometimes suffice to nearly eliminate binding; for example, the aminoacyl tRNA synthetase specific to the amino acid valine discriminates against the very similar side chain of the amino acid isoleucine.^[29]

Proteins can bind to other proteins as well as to small-molecule substrates. When proteins bind specifically to other copies of the same molecule, they can oligomerize to form fibrils; this process occurs often in structural proteins that consist of globular monomers that self-associate to form rigid fibers. Protein–protein interactions also regulate enzymatic activity, control progression through the cell cycle, and allow the assembly of large protein complexes that carry out many closely related reactions with a common biological function. Proteins can also bind to, or even be integrated into, cell membranes. The ability of binding partners to induce conformational changes in proteins allows the construction of enormously complex signaling networks.^[30] Importantly, as interactions between proteins are reversible, and depend heavily on the availability of different groups of partner proteins to form aggregates that are capable to carry out discrete sets of function, study of the interactions between specific proteins is a key to understand important aspects of cellular function, and ultimately the properties that distinguish particular cell types.^{[31] [32]}

Enzymes

The best-known role of proteins in the cell is as enzymes, which catalyze chemical reactions. Enzymes are usually highly specific and accelerate only one or a few chemical reactions. Enzymes carry out most of the reactions involved in metabolism, as well as manipulating DNA in processes such as DNA replication, DNA repair, and transcription. Some enzymes act on other proteins to add or remove chemical groups in a process known as post-translational modification. About 4,000 reactions are known to be catalyzed by enzymes.^[33] The rate acceleration conferred by enzymatic catalysis is often enormous—as much as 10^{17} -fold increase in rate over the uncatalyzed reaction in the case of orotate decarboxylase (78 million years without the enzyme, 18 milliseconds with the enzyme).^[34]

The molecules bound and acted upon by enzymes are called substrates. Although enzymes can consist of hundreds of amino acids, it is usually only a small fraction of the residues that come in contact with the substrate, and an even smaller fraction—three to four residues on average—that are directly involved in catalysis.^[35] The region of the enzyme that binds the substrate and contains the catalytic residues is known as the active site.

Cell signaling and ligand binding

Many proteins are involved in the process of cell signaling and signal transduction. Some proteins, such as insulin, are extracellular proteins that transmit a signal from the cell in which they were synthesized to other cells in distant tissues. Others are membrane proteins that act as receptors whose main function is to bind a signaling molecule and induce a biochemical response in the cell. Many receptors have a binding site exposed on the cell surface and an effector domain within the cell, which may have enzymatic activity or may undergo a conformational change detected by other proteins within the cell.^[36]

Antibodies are protein components of adaptive immune system whose main function is to bind antigens, or foreign substances in the body, and target them for destruction. Antibodies can be secreted into the extracellular environment or anchored in the membranes of specialized B cells known as plasma cells. Whereas enzymes are limited in their binding affinity for their substrates by the necessity of conducting their reaction, antibodies have no such constraints. An antibody's binding affinity to its target is extraordinarily high.^[37]

Many ligand transport proteins bind particular small biomolecules and transport them to other locations in the body of a multicellular organism. These proteins must have a high binding affinity when their ligand is present in high concentrations, but must also release the ligand when it is present at low concentrations in the target tissues. The canonical example of a ligand-binding protein is haemoglobin, which transports oxygen from the lungs to other organs and tissues in all vertebrates and has close homologs in every biological kingdom.^[38] Lectins are sugar-binding proteins which are highly specific for their sugar moieties. Lectins typically play a role in biological recognition phenomena involving cells and proteins.^[39] Receptors and hormones are highly specific binding proteins.

Transmembrane proteins can also serve as ligand transport proteins that alter the permeability of the cell membrane to small molecules and ions. The membrane alone has a hydrophobic core through which polar or charged molecules cannot diffuse. Membrane proteins contain internal channels that allow such molecules to enter and exit the cell. Many ion channel proteins are specialized to select for only a particular ion; for example, potassium and sodium channels often discriminate for only one of the two ions.^[40]

Structural proteins

Structural proteins confer stiffness and rigidity to otherwise-fluid biological components. Most structural proteins are fibrous proteins; for example, actin and tubulin are globular and soluble as monomers, but polymerize to form long, stiff fibers that comprise the cytoskeleton, which allows the cell to maintain its shape and size. Collagen and elastin are critical components of connective tissue such as cartilage, and keratin is found in hard or filamentous structures such as hair, nails, feathers, hooves, and some animal shells.^[41]

Other proteins that serve structural functions are motor proteins such as myosin, kinesin, and dynein, which are capable of generating mechanical forces. These proteins are crucial for cellular motility of single celled organisms and the sperm of many multicellular organisms which reproduce sexually. They also generate the forces exerted by contracting muscles.^[42]



Methods of study

As some of the most commonly studied biological molecules, the activities and structures of proteins are examined both *in vitro* and *in vivo*. *In vitro* studies of purified proteins in controlled environments are useful for learning how a protein carries out its function: for example, enzyme kinetics studies explore the chemical mechanism of an enzyme's catalytic activity and its relative affinity for various possible substrate molecules. By contrast, *in vivo* experiments on proteins' activities within cells or even within whole organisms can provide complementary information about where a protein functions and how it is regulated.

Protein purification

In order to perform *in vitro* analysis, a protein must be purified away from other cellular components. This process usually begins with cell lysis, in which a cell's membrane is disrupted and its internal contents released into a solution known as a crude lysate. The resulting mixture can be purified using ultracentrifugation, which fractionates the various cellular components into fractions containing soluble proteins; membrane lipids and proteins; cellular organelles, and nucleic acids. Precipitation by a method known as salting out can concentrate the proteins from this lysate. Various types of chromatography are then used to isolate the protein or proteins of interest based on properties such as molecular weight, net charge and binding affinity.^[43] The level of purification can be monitored using various types of gel electrophoresis if the desired protein's molecular weight and isoelectric point are known, by spectroscopy if the protein has distinguishable spectroscopic features, or by enzyme assays if the protein has enzymatic activity. Additionally, proteins can be isolated according to their charge using electrofocusing.^[44]

For natural proteins, a series of purification steps may be necessary to obtain protein sufficiently pure for laboratory applications. To simplify this process, genetic engineering is often used to add chemical features to proteins that make them easier to purify without affecting their structure or activity. Here, a "tag" consisting of a specific amino acid sequence, often a series of histidine residues (a "His-tag"), is attached to one terminus of the protein. As a result, when the lysate is passed over a chromatography column containing nickel, the histidine residues ligate the nickel and attach to the column while the untagged components of the lysate pass unimpeded. A number of different tags have been developed to help researchers purify specific proteins from complex mixtures.^[45]

Cellular localization

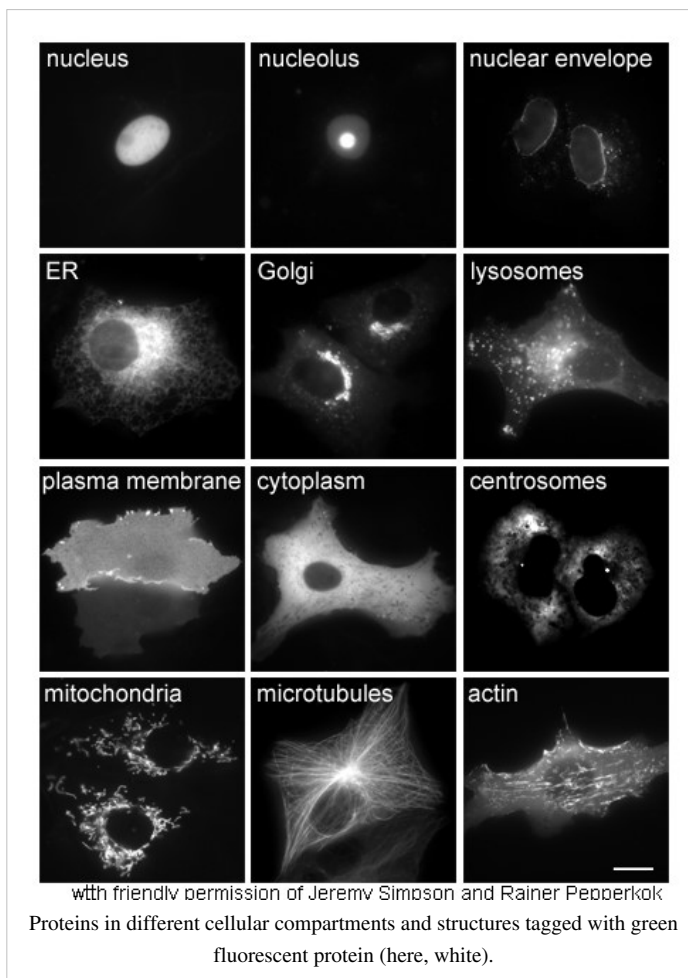
The study of proteins *in vivo* is often concerned with the synthesis and localization of the protein within the cell. Although many intracellular proteins are synthesized in the cytoplasm and membrane-bound or secreted proteins in the endoplasmic reticulum, the specifics of how proteins are targeted to specific organelles or cellular structures is often unclear. A useful technique for assessing cellular localization uses genetic engineering to express in a cell a fusion protein or chimera consisting of the natural protein of interest linked to a "reporter" such as green fluorescent protein (GFP).^[46] The fused protein's position within the cell can be cleanly and efficiently visualized using microscopy,^[47] as shown in the figure opposite.

Other methods for elucidating the cellular location of proteins requires the use of known compartmental markers for regions such as the ER, the Golgi, lysosomes/vacuoles, mitochondria, chloroplasts, plasma membrane, etc. With the use of fluorescently tagged versions of these markers or of antibodies to known markers, it becomes much simpler to identify the localization of a protein of interest. For example, indirect immunofluorescence will allow for fluorescence colocalization and demonstration of location. Fluorescent dyes are used to label cellular compartments for a similar purpose.^[48]

Other possibilities exist, as well. For example, immunohistochemistry usually utilizes an antibody to one or more proteins of interest that are conjugated to enzymes yielding either luminescent or chromogenic signals that can be compared between samples, allowing for localization information. Another applicable technique is cofractionation in sucrose (or other material) gradients using isopycnic centrifugation.^[49] While this technique does not prove colocalization of a compartment of known density and the protein of interest, it does increase the likelihood, and is more amenable to large-scale studies.

Finally, the gold-standard method of cellular localization is immunoelectron microscopy. This technique also uses an antibody to the protein of interest, along with classical electron microscopy techniques. The sample is prepared for normal electron microscopic examination, and then treated with an antibody to the protein of interest that is conjugated to an extremely electro-dense material, usually gold. This allows for the localization of both ultrastructural details as well as the protein of interest.^[50]

Through another genetic engineering application known as site-directed mutagenesis, researchers can alter the protein sequence and hence its structure, cellular localization, and susceptibility to regulation. This technique even allows the incorporation of unnatural amino acids into proteins, using modified tRNAs,^[51] and may allow the rational design of new proteins with novel properties.^[52]



Proteomics and bioinformatics

The total complement of proteins present at a time in a cell or cell type is known as its proteome, and the study of such large-scale data sets defines the field of proteomics, named by analogy to the related field of genomics. Key experimental techniques in proteomics include 2D electrophoresis,^[53] which allows the separation of a large number of proteins, mass spectrometry,^[54] which allows rapid high-throughput identification of proteins and sequencing of peptides (most often after in-gel digestion), protein microarrays,^[55] which allow the detection of the relative levels of a large number of proteins present in a cell, and two-hybrid screening, which allows the systematic exploration of protein–protein interactions.^[56] The total complement of biologically possible such interactions is known as the interactome.^[57] A systematic attempt to determine the structures of proteins representing every possible fold is known as structural genomics.^[58]

The large amount of genomic and proteomic data available for a variety of organisms, including the human genome, allows researchers to efficiently identify homologous proteins in distantly related organisms by sequence alignment. Sequence profiling tools can perform more specific sequence manipulations such as restriction enzyme maps, open reading frame analyses for nucleotide sequences, and secondary structure prediction. From this data phylogenetic trees can be constructed and evolutionary hypotheses developed using special software like ClustalW regarding the ancestry of modern organisms and the genes they express. The field of bioinformatics seeks to assemble, annotate, and analyze genomic and proteomic data, applying computational techniques to biological problems such as gene finding and cladistics.

Structure prediction and simulation

Complementary to the field of structural genomics, protein structure prediction seeks to develop efficient ways to provide plausible models for proteins whose structures have not yet been determined experimentally.^[59] The most successful type of structure prediction, known as homology modeling, relies on the existence of a "template" structure with sequence similarity to the protein being modeled; structural genomics' goal is to provide sufficient representation in solved structures to model most of those that remain.^[60] Although producing accurate models remains a challenge when only distantly related template structures are available, it has been suggested that sequence alignment is the bottleneck in this process, as quite accurate models can be produced if a "perfect" sequence alignment is known.^[61] Many structure prediction methods have served to inform the emerging field of protein engineering, in which novel protein folds have already been designed.^[62] A more complex computational problem is the prediction of intermolecular interactions, such as in molecular docking and protein–protein interaction prediction.^[63]

The processes of protein folding and binding can be simulated using such technique as molecular mechanics, in particular, molecular dynamics and Monte Carlo, which increasingly take advantage of parallel and distributed computing (Folding@Home project,^[64] molecular modeling on GPU). The folding of small alpha-helical protein domains such as the villin headpiece^[65] and the HIV accessory protein^[66] have been successfully simulated *in silico*, and hybrid methods that combine standard molecular dynamics with quantum mechanics calculations have allowed exploration of the electronic states of rhodopsins.^[67]

Nutrition

Most microorganisms and plants can biosynthesize all 20 standard amino acids, while animals (including humans) must obtain some of the amino acids from the diet.^[28] The amino acids that an organism cannot synthesize on its own are referred to as essential amino acids. Key enzymes that synthesize certain amino acids are not present in animals — such as aspartokinase, which catalyzes the first step in the synthesis of lysine, methionine, and threonine from aspartate. If amino acids are present in the environment, microorganisms can conserve energy by taking up the amino acids from their surroundings and downregulating their biosynthetic pathways.

In animals, amino acids are obtained through the consumption of foods containing protein. Ingested proteins are then broken down into amino acids through digestion, which typically involves denaturation of the protein through exposure to acid and hydrolysis by enzymes called proteases. Some ingested amino acids are used for protein biosynthesis, while others are converted to glucose through gluconeogenesis, or fed into the citric acid cycle. This use of protein as a fuel is particularly important under starvation conditions as it allows the body's own proteins to be used to support life, particularly those found in muscle.^[68] Amino acids are also an important dietary source of nitrogen.

History and etymology

Proteins were recognized as a distinct class of biological molecules in the eighteenth century by Antoine Fourcroy and others, distinguished by the molecules' ability to coagulate or flocculate under treatments with heat or acid. Noted examples at the time included albumin from egg whites, blood serum albumin, fibrin, and wheat gluten. Dutch chemist Gerhardus Johannes Mulder carried out elemental analysis of common proteins and found that nearly all proteins had the same empirical formula, $C_{400}H_{620}N_{100}O_{120}P_1S_1$.^[69] He came to the erroneous conclusion that they might be composed of a single type of (very large) molecule. The term "protein" to describe these molecules was proposed in 1838 by Mulder's associate Jöns Jakob Berzelius; protein is derived from the Greek word *πρωτεῖος* (*proteios*), meaning "primary",^[70] "in the lead", or "standing in front".^[71] Mulder went on to identify the products of protein degradation such as the amino acid leucine for which he found a (nearly correct) molecular weight of 131 Da.^[69]

The difficulty in purifying proteins in large quantities made them very difficult for early protein biochemists to study. Hence, early studies focused on proteins that could be purified in large quantities, e.g., those of blood, egg white, various toxins, and digestive/metabolic enzymes obtained from slaughterhouses. In the 1950s, the Armour Hot Dog Co. purified 1 kg of pure bovine pancreatic ribonuclease A and made it freely available to scientists; this gesture helped ribonuclease A become a major target for biochemical study for the following decades.^[69]

Linus Pauling is credited with the successful prediction of regular protein secondary structures based on hydrogen bonding, an idea first put forth by William Astbury in 1933.^[72] Later work by Walter Kauzmann on denaturation,^[73]^[74] based partly on previous studies by Kaj Linderstrøm-Lang,^[75] contributed an understanding of protein folding and structure mediated by hydrophobic interactions. In 1949 Fred Sanger correctly determined the amino acid sequence of insulin, thus conclusively demonstrating that proteins consisted of linear polymers of amino acids rather than branched chains, colloids, or cyclols.^[76] The first atomic-resolution structures of proteins were solved by X-ray crystallography in the 1960s^[1] and by NMR in the 1980s.^[1] As of 2009, the Protein Data Bank has over 55,000 atomic-resolution structures of proteins.^[77] In more recent times, cryo-electron microscopy of large macromolecular assemblies^[78] and computational protein structure prediction of small protein domains^[79] are two methods approaching atomic resolution.

Footnotes

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External links

- Protein Songs (Stuart Mitchell – DNA Music Project) (<http://www.tjmitchell.com/stuart/dna.html>), 'When a "tape" of mRNA passes through the "playing head" of a ribosome, the "notes" produced are amino acids and the pieces of music they make up are proteins.'

Databases and projects

- Comparative Toxicogenomics Database (<http://ctd.mdibl.org/>) curates protein–chemical interactions, as well as gene/protein–disease relationships and chemical–disease relationships.
- Bioinformatic Harvester (<http://harvester.fzk.de>) A Meta search engine (29 databases) for gene and protein information.
- The Protein Databank (<http://www.rcsb.org>) (see also PDB Molecule of the Month (http://www.rcsb.org/pdb/static.do?p=education_discussion/molecule_of_the_month/index.html), presenting short accounts on selected proteins from the PDB)
- Proteopedia – Life in 3D (<http://www.proteopedia.org>): rotatable, zoomable 3D model with wiki annotations for every known protein molecular structure.
- UniProt the Universal Protein Resource (<http://www.expasy.uniprot.org>)

- The Protein Naming Utility (<http://www.jcvi.org/pn-utility>)
- Human Protein Atlas (<http://www.proteinatlas.org>)
- NCBI Entrez Protein database (<http://www.ncbi.nlm.nih.gov/sites/entrez?db=protein>)
- NCBI Protein Structure database (<http://www.ncbi.nlm.nih.gov/sites/entrez?db=structure>)
- Human Protein Reference Database (<http://www.hprd.org/>)
- Human Proteinpedia (<http://www.humanproteinpedia.org/>)
- Folding@Home (Stanford University) (<http://folding.stanford.edu/>)

Tutorials and educational websites

- "An Introduction to Proteins" (<http://hopes.stanford.edu/basics/proteins/p0.html>) from HOPES (Huntington's Disease Outreach Project for Education at Stanford)
- Proteins: Biogenesis to Degradation – The Virtual Library of Biochemistry and Cell Biology (<http://www.biochemweb.org/proteins.shtml>)

Protein structure

Proteins are an important class of biological macromolecules present in all organisms. All proteins are polymers of amino acids. Classified by their physical size, proteins are nanoparticles (definition: 1-100 nm). Each protein polymer – also known as a polypeptide – consists of a sequence of 20 different L- α -amino acids, also referred to as residues. For chains under 40 residues the term peptide is frequently used instead of protein. To be able to perform their biological function, proteins fold into one or more specific spatial conformations, driven by a number of non-covalent interactions such as hydrogen bonding, ionic interactions, Van Der Waals forces, and hydrophobic packing. To understand the functions of proteins at a molecular level, it is often necessary to determine their three-dimensional structure. This is the topic of the scientific field of structural biology, which employs techniques such as X-ray crystallography, NMR spectroscopy, and dual polarisation interferometry to determine the structure of proteins.

Protein structures range in size from tens to several thousand residues^[1] Very large aggregates can be formed from protein subunits: for example, many thousand actin molecules assemble into a microfilament.

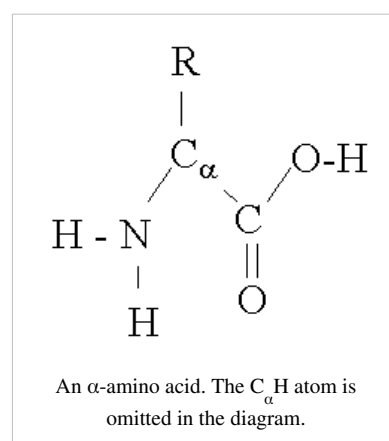
A protein may undergo reversible structural changes in performing its biological function. The alternative structures of the same protein are referred to as different conformations, and transitions between them are called conformational changes.

Protein covalent structure and stereochemistry

Protein amino acids are combined into a single polypeptide chain in a condensation reaction. This reaction is catalysed by the ribosome in a process known as translation.

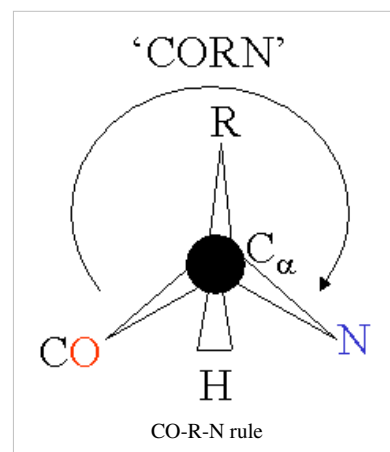
Amino acid residues

Each α -amino acid consists of a backbone part that is present in all the amino acid types, and a side chain that is unique to each type of residue. An exception from this rule is proline, where the hydrogen atom is replaced by a bond to the side chain. Because the carbon atom is bound to four different



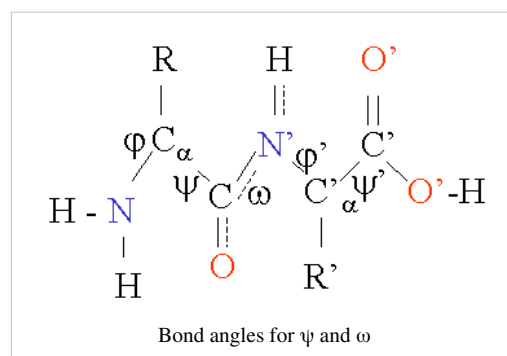
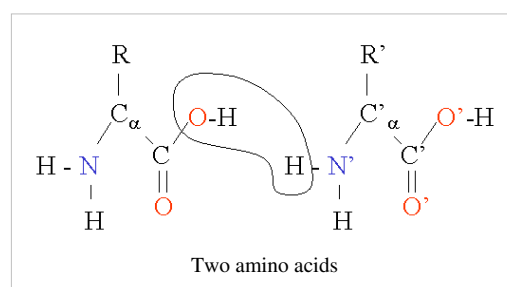
groups it is chiral, however only one of the isomers occur in biological proteins. Glycine however, is not chiral since its side chain is a hydrogen atom. A simple mnemonic for correct L-form is "CORN": when the C_α atom is viewed with the H in front, the residues read "CO-R-N" in a clockwise direction.

The 20 naturally occurring amino acids have different physical and chemical properties, including their electrostatic charge, pKa, hydrophobicity, size and specific functional groups. These properties play a major role in molding protein structure.



The peptide bond

The peptide bond tends to be planar due to the delocalization of the electrons from the double bond. The rigid peptide dihedral angle, ω (the bond between C_1 and N) is always close to 180 degrees. The dihedral angles phi ϕ (the bond between N and C_α) and psi ψ (the bond between C_α and C_1) can have a certain range of possible values. These angles are the internal degrees of freedom of a protein, they control the protein's conformation. They are restrained by geometry to allowed ranges typical for particular secondary structure elements, and represented in a Ramachandran plot. A few important bond lengths are given in the table below.



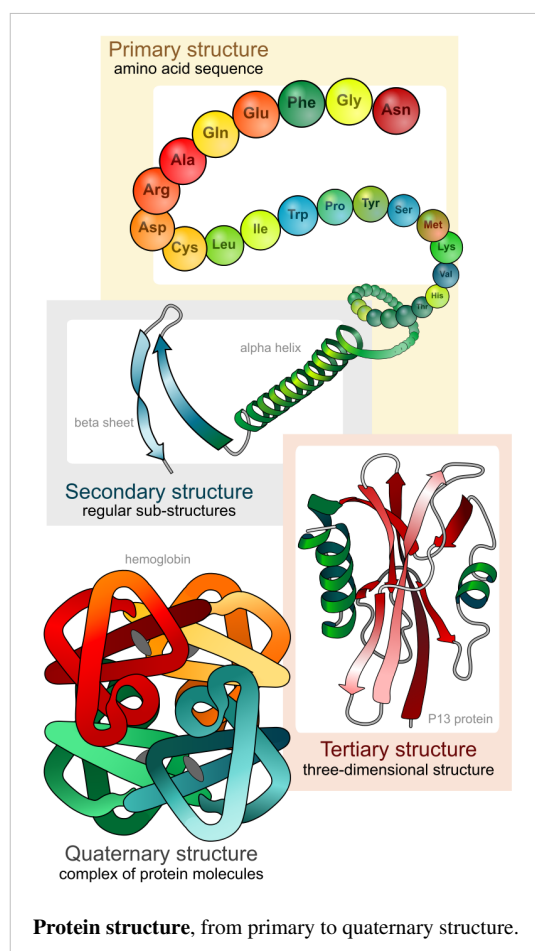
Peptide bond	Average length	Single bond	Average length	Hydrogen bond	Average (± 30)
Ca - C	153 pm	C - C	154 pm	O-H --- O-H	280 pm
C - N	133 pm	C - N	148 pm	N-H --- O=C	290 pm
N - Ca	146 pm	C - O	143 pm	O-H --- O=C	280 pm

Side-chain conformation

The atoms along the side chain are named with Greek letters in Greek alphabetical order: α , β , γ , δ , ϵ , and so on. C_α refers to the carbon atom of the backbone closest to the carbonyl group of that amino acid, C_β the second closest and so on. The dihedral angles around the bonds between these atoms are named χ_1 , χ_2 , χ_3 , etc. The dihedral angle of the first movable atom of the side chain, γ , defined as N-C α -C β -X γ , is named χ_1 . Side chains tend to adopt different staggered conformations called *gauche*(-), *trans*, and *gauche*(+), which corresponds to rotation angles of 60°, 180°, and -60°, respectively, around the sp³-sp³ bonds.

The diversity of side-chain conformations is often expressed in rotamer libraries. A rotamer library is a collection of rotamers for each residue type. Side-chain dihedral angles are not evenly distributed, but for most side chain types, the χ angles occur in tight clusters around certain values. Rotamer libraries therefore are usually derived from statistical analysis of side-chain conformations in known structures of proteins by clustering observed conformations or by dividing dihedral angle space into bins, and determining an average conformation in each bin^{[2] [3]}.

Levels of protein structure



There are four distinct levels of protein structure.

Primary structure

The primary structure refers to the sequence of the different amino acids of the peptide or protein. The primary structure is held together by covalent or peptide bonds, which are made during the process of protein biosynthesis or translation. The two ends of the polypeptide chain are referred to as the carboxyl terminus (C-terminus) and the amino terminus (N-terminus) based on the nature of the free group on each extremity. Counting of residues always starts at the N-terminal end (NH_2 -group), which is the end where the amino group is involved in a peptide bond. The primary structure of a protein is determined by the gene corresponding to the protein. A specific sequence of nucleotides in DNA is transcribed into mRNA, which is read by the ribosome in a process called translation. The sequence of a protein is unique to that protein, and defines the structure and function of the protein. The sequence of a protein can be determined by methods such as Edman degradation or tandem mass spectrometry. Often however, it is read directly from the sequence of the gene using the genetic code. Post-translational modifications such as disulfide formation, phosphorylations and glycosylations are usually also

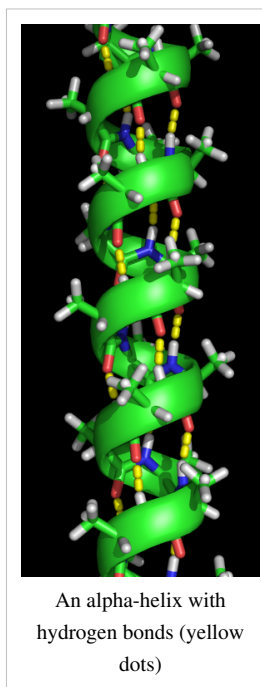
considered a part of the primary structure, and cannot be read from the gene.

Secondary structure

Secondary structure refers to highly regular local sub-structures. Two main types of secondary structure, the alpha helix and the beta strand, were suggested in 1951 by Linus Pauling and coworkers.^[4] These secondary structures are defined by patterns of hydrogen bonds between the main-chain peptide groups. They have a regular geometry, being constrained to specific values of the dihedral angles ψ and ϕ on the Ramachandran plot. Both the alpha helix and the beta-sheet represent a way of saturating all the hydrogen bond donors and acceptors in the peptide backbone. Some parts of the protein are ordered but do not form any regular structures. They should not be confused with random coil, an unfolded polypeptide chain lacking any fixed three-dimensional structure. Several sequential secondary structures may form a "supersecondary unit".^[5]

Tertiary structure

Tertiary structure refers to three-dimensional structure of a single protein molecule. The alpha-helices and beta-sheets are folded into a compact globule. The folding is driven by the *non-specific* hydrophobic interactions (the burial of hydrophobic residues from water), but the structure is stable only when the parts of a protein domain are locked into place by *specific* tertiary interactions, such as salt bridges, hydrogen bonds, and the tight packing of side chains and disulfide bonds. The disulfide bonds are extremely rare in cytosolic proteins, since the cytosol is generally a reducing environment.



Quaternary structure

Quaternary structure is a larger assembly of several protein molecules or polypeptide chains, usually called subunits in this context. The quaternary structure is stabilized by the same non-covalent interactions and disulfide bonds as the tertiary structure. Complexes of two or more polypeptides (i.e. multiple subunits) are called multimers. Specifically it would be called a dimer if it contains two subunits, a trimer if it contains three subunits, and a tetramer if it contains four subunits. The subunits are frequently related to one another by symmetry operations, such as a 2-fold axis in a dimer. Multimers made up of identical subunits are referred to with a prefix of "homo-" (e.g. a homotetramer) and those made up of different subunits are referred to with a prefix of "hetero-" (e.g. a heterotetramer, such as the two alpha and two beta chains of hemoglobin). Many proteins do not have the quaternary structure and function as monomers.

Domains, motifs, and folds in protein structure

Proteins are frequently described as consisting from several structural units.

- A **structural domain** is an element of the protein's overall structure that is self-stabilizing and often folds independently of the rest of the protein chain. Many domains are not unique to the protein products of one gene or one gene family but instead appear in a variety of proteins. Domains often are named and singled out because they figure prominently in the biological function of the protein they belong to; for example, the "calcium-binding domain of calmodulin". Because they are independently stable, domains can be "swapped" by genetic engineering between one protein and another to make chimeras.
- The **structural and sequence motifs** refer to short segments of protein three-dimensional structure or amino acid sequence that were found in a large number of different proteins.

- The **supersecondary structure** refers to a specific combination of secondary structure elements, such as beta-alpha-beta units or helix-turn-helix motif. Some of them may be also referred to as structural motifs.
- **Protein fold** refers to the general protein architecture, like helix bundle, beta-barrel, Rossman fold or different "folds" provided in the Structural Classification of Proteins database^[6].

Despite the fact that there are about 100,000 different proteins expressed in eukaryotic systems, there are many fewer different domains, structural motifs and folds. This is partly a consequence of evolution, since genes or parts of genes can be doubled or moved around within the genome. This means that, for example, a protein domain might be moved from one protein to another thus giving the protein a new function. Because of these mechanisms, pathways and mechanisms tend to be reused in several different proteins.

Protein folding

An unfolded polypeptide folds into its characteristic three-dimensional structure from random coil.

Protein structure determination

Around 90% of the protein structures available in the Protein Data Bank have been determined by X-ray crystallography. This method allows one to measure the 3D density distribution of electrons in the protein (in the crystallized state) and thereby infer the 3D coordinates of all the atoms to be determined to a certain resolution. Roughly 9% of the known protein structures have been obtained by Nuclear Magnetic Resonance techniques. The secondary structure composition can be determined via circular dichroism or dual polarisation interferometry. Cryo-electron microscopy has recently become a means of determining protein structures to high resolution (less than 5 angstroms or 0.5 nanometer) and is anticipated to increase in power as a tool for high resolution work in the next decade. This technique is still a valuable resource for researchers working with very large protein complexes such as virus coat proteins and amyloid fibers.

Structure classification

Protein structures can be classified based on their similarity or a common evolutionary origin. SCOP and CATH databases provide two different structural classifications of proteins.

Computational prediction of protein structure

The generation of a protein sequence is much easier than the determination of a protein structure. However, the structure of a protein gives much more insight in the function of the protein than its sequence. Therefore, a number of methods for the computational prediction of protein structure from its sequence have been developed^[7]. *Ab initio* prediction methods use just the sequence of the protein. Threading and Homology Modeling methods can build a 3D model for a protein of unknown structure from experimental structures of evolutionary related proteins.

Protein structure related software

There are software to aid researchers working on, often overlapping, different aspects of protein structure. The most basic functionality is providing structure visualization. Analysis of protein structure can be facilitated by software that aligns structures. In the absence of existing structures for a given protein sequence, there are methods to predict or to model the structure of such sequences based on known protein structures. And given models of known or predicted structures, one can use software to verify them for errors, predict protein conformational changes, or predict substrate binding sites.

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Further reading

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External links

Wikis

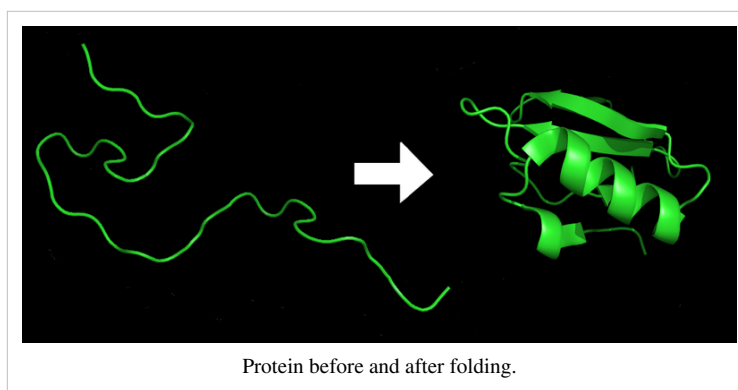
- PDBWiki (<http://pdwiki.org>) — A discussion forum for macromolecular structures (see PDBWiki)
- Proteopedia (<http://www.proteopedia.org>) — Annotation of protein structures and other biomolecules
- TOPSAN (<http://www.topsan.org>) — Annotation of protein structures in Structural genomics

Servers

- SSS Database (<http://binfs.umdj.edu/sssdb/>) — super-secondary structure protein database
- SPROUTS (<http://bioinformatics.eas.asu.edu/springs/Sprouts/projectsSprouts.html>) (Structural Prediction for pRotein fOlding UTility System)
- ProSA-web (<https://prosa.services.came.sbg.ac.at/prosa.php>) — a web service for the recognition of errors in experimentally or theoretically determined protein structures
- NQ-Flipper (<https://flipper.services.came.sbg.ac.at/>) — checks for unfavorable rotamers of Asn and Gln residues in protein structures
- WHAT IF servers (<http://swift.cmbi.ru.nl/>) — checks nearly 200 aspects of protein structure, like packing, geometry, unfavourable rotamers in general of for Asn, Gln, and His especially, strange water molecules, backbone conformations, atom nomenclature, symmetry parameters, etc.

Protein folding

Protein folding is the physical process by which a polypeptide folds into its characteristic and functional three-dimensional structure from random coil.^[1] Each protein exists as an unfolded polypeptide or random coil when translated from a sequence of mRNA to a linear chain of amino acids. This polypeptide lacks any developed three-dimensional structure (the left hand side of the neighboring figure). Amino acids interact with each other to produce a well-defined three-dimensional structure, the folded protein (the right hand side of the figure), known as the native state. The resulting three-dimensional structure is determined by the amino acid sequence (Anfinsen's dogma).^[2]



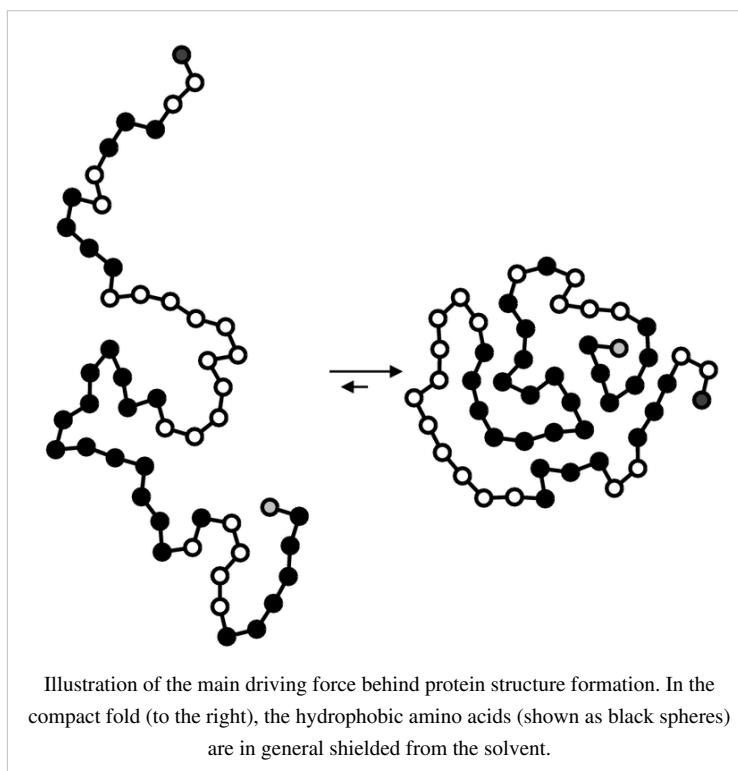
The correct three-dimensional structure is essential to function, although some parts of functional proteins may remain unfolded.^[3] Failure to fold into the intended shape usually produces inactive proteins with different properties including toxic prions. Several neurodegenerative and other diseases are believed to result from the accumulation of *misfolded* (incorrectly folded) proteins.^[4] Many allergies are caused by the folding of the proteins, for the immune system does not produce antibodies for certain protein structures.^[5]

Known facts

Relationship between folding and amino acid sequence

The amino-acid sequence (or primary structure) of a protein determines its native conformation.^[6] A protein molecule folds spontaneously during or after biosynthesis. While these macromolecules may be regarded as "folding themselves", the process also depends on the solvent (water or lipid bilayer),^[7] the concentration of salts, the temperature, and the presence of molecular chaperones.

Folded proteins usually have a hydrophobic core in which side chain packing stabilizes the folded state, and charged or polar side chains occupy the solvent-exposed surface where they interact with surrounding water. Minimizing the number of hydrophobic side-chains exposed to water is an important driving force behind the folding process.^[8]



Formation of intramolecular hydrogen bonds provides another important contribution to protein stability.^[9] The strength of hydrogen bonds depends on their environment, thus H-bonds enveloped in a hydrophobic core contribute more than H-bonds exposed to the aqueous environment to the stability of the native state.^[10]

The process of folding *in vivo* often begins co-translationally, so that the N-terminus of the protein begins to fold while the C-terminal portion of the protein is still being synthesized by the ribosome. Specialized proteins called chaperones assist in the folding of other proteins.^[11] A well studied example is the bacterial GroEL system, which assists in the folding of globular proteins. In eukaryotic organisms chaperones are known as heat shock proteins. Although most globular proteins are able to assume their native state unassisted, chaperone-assisted folding is often necessary in the crowded intracellular environment to prevent aggregation; chaperones are also used to prevent misfolding and aggregation which may occur as a consequence of exposure to heat or other changes in the cellular environment.

There are two models of protein folding that are currently being confirmed. The first is the diffusion collision model in which a nuclei is formed, then the secondary structure, and finally these secondary structures are collided together and pack tightly together. The next model is the nucleation-condensation model, in which the secondary and tertiary structure of the protein is made at the same time. Finally, recent studies have shown that some proteins show characteristics of both of these folding models.

For the most part, scientists have been able to study many identical molecules folding together *en masse*. At the coarsest level, it appears that in transitioning to the native state, a given amino acid sequence takes on roughly the same route and proceeds through roughly the same intermediates and transition states. Often folding involves first the establishment of regular secondary and supersecondary structures, particularly alpha helices and beta sheets, and afterwards tertiary structure. Formation of quaternary structure usually involves the "assembly" or "coassembly" of subunits that have already folded. The regular alpha helix and beta sheet structures fold rapidly because they are stabilized by intramolecular hydrogen bonds, as was first characterized by Linus Pauling. Protein folding may involve covalent bonding in the form of disulfide bridges formed between two cysteine residues or the formation of metal clusters. Shortly before settling into their more energetically favourable native conformation, molecules may pass through an intermediate "molten globule" state.

The essential fact of folding, however, remains that the amino acid sequence of each protein contains the information that specifies both the native structure and the pathway to attain that state. This is not to say that nearly identical amino acid sequences always fold similarly.^[12] Conformations differ based on environmental factors as well; similar proteins fold differently based on where they are found. Folding is a spontaneous process independent of energy inputs from nucleoside triphosphates. The passage of the folded state is mainly guided by hydrophobic interactions, formation of intramolecular hydrogen bonds, and van der Waals forces, and it is opposed by conformational entropy.

Disruption of the native state

Under some conditions proteins will not fold into their biochemically functional forms. Temperatures above or below the range that cells tend to live in will cause thermally unstable proteins to unfold or "denature" (this is why boiling makes an egg white turn opaque). High concentrations of solutes, extremes of pH, mechanical forces, and the presence of chemical denaturants can do the same. Protein thermal stability is far from constant, however. For example, hyperthermophilic bacteria have been found that grow at temperatures as high as 122 °C,^[13] which of course requires that their full complement of vital proteins and protein assemblies be stable at that temperature or above.

A fully denatured protein lacks both tertiary and secondary structure, and exists as a so-called random coil. Under certain conditions some proteins can refold; however, in many cases denaturation is irreversible.^[14] Cells sometimes protect their proteins against the denaturing influence of heat with enzymes known as chaperones or heat shock proteins, which assist other proteins both in folding and in remaining folded. Some proteins never fold in cells at all except with the assistance of chaperone molecules, which either isolate individual proteins so that their folding is not

interrupted by interactions with other proteins or help to unfold misfolded proteins, giving them a second chance to refold properly. This function is crucial to prevent the risk of precipitation into insoluble amorphous aggregates.

Incorrect protein folding and neurodegenerative disease

Aggregated proteins are associated with prion-related illnesses such as Creutzfeldt-Jakob disease, bovine spongiform encephalopathy (mad cow disease), amyloid-related illnesses such as Alzheimer's disease and familial amyloid cardiomyopathy or polyneuropathy, as well as intracytoplasmic aggregation diseases such as Huntington's and Parkinson's disease.^{[4] [15]} These age onset degenerative diseases are associated with the multimerization of misfolded proteins into insoluble, extracellular aggregates and/or intracellular inclusions including cross-beta sheet amyloid fibrils; it is not clear whether the aggregates are the cause or merely a reflection of the loss of protein homeostasis, the balance between synthesis, folding, aggregation and protein turnover. Misfolding and excessive degradation instead of folding and function leads to a number of proteopathy diseases such as antitrypsin-associated emphysema, cystic fibrosis and the lysosomal storage diseases, where loss of function is the origin of the disorder. While protein replacement therapy has historically been used to correct the latter disorders, an emerging approach is to use pharmaceutical chaperones to fold mutated proteins to render them functional.

The Levinthal paradox and kinetics

The Levinthal paradox^[16] observes that if a protein were to fold by sequentially sampling all possible conformations, it would take an astronomical amount of time to do so, even if the conformations were sampled at a rapid rate (on the nanosecond or picosecond scale). Based upon the observation that proteins fold much faster than this, Levinthal then proposed that a random conformational search does not occur, and the protein must, therefore, fold through a series of meta-stable intermediate states.

The duration of the folding process varies dramatically depending on the protein of interest. When studied outside the cell, the slowest folding proteins require many minutes or hours to fold primarily due to proline isomerization, and must pass through a number of intermediate states, like checkpoints, before the process is complete.^[17] On the other hand, very small single-domain proteins with lengths of up to a hundred amino acids typically fold in a single step.^[18] Time scales of milliseconds are the norm and the very fastest known protein folding reactions are complete within a few microseconds.^[19]

Energy landscape theory of protein folding

The protein folding phenomenon was largely an experimental endeavor until the formulation of an energy landscape theory of proteins by Joseph Bryngelson and Peter Wolynes in the late 1980s and early 1990s. This approach introduced the *principle of minimal frustration*,^[20] which asserts that evolution has selected the amino acid sequences of natural proteins so that interactions between side chains largely favor the molecule's acquisition of the folded state. Interactions that do not favor folding are selected against, although some residual *frustration* is expected to exist. A consequence of these evolutionarily selected sequences is that proteins are generally thought to have globally "funneled energy landscapes" (coined by José Onuchic)^[21] that are largely directed towards the native state. This "folding funnel" landscape allows the protein to fold to the native state through any of a large number of pathways and intermediates, rather than being restricted to a single mechanism. The theory is supported by both computational simulations of model proteins and experimental studies,^[20] and it has been used to improve methods for protein structure prediction and design.^[20] The description of protein folding by the leveling free-energy landscape is also consistent with the 2nd law of thermodynamics.^[22]

Techniques for studying protein folding

Circular dichroism

Circular dichroism is one of the most general and basic tools to study protein folding. Circular dichroism spectroscopy measures the absorption of circularly polarized light. In proteins, structures such as alpha helices and beta sheets are chiral, and thus absorb such light. The absorption of this light acts as a marker of the degree of foldedness of the protein ensemble. This technique can be used to measure equilibrium unfolding of the protein by measuring the change in this absorption as a function of denaturant concentration or temperature. A denaturant melt measures the free energy of unfolding as well as the protein's m value, or denaturant dependence. A temperature melt measures the melting temperature (T_m) of the protein. This type of spectroscopy can also be combined with fast-mixing devices, such as stopped flow, to measure protein folding kinetics and to generate chevron plots.

Dual Polarisation Interferometry

Dual polarisation interferometry is a surface based technique for measuring the optical properties of molecular layers. When used to characterise protein folding, it measures the conformation by determining the overall size of a monolayer of the protein and its density in real time at sub-Angstrom resolution. Although real time, measurement of the kinetics of protein folding are limited to processes that occur slower than ~ 10 Hz. Similar to circular dichroism the stimulus for folding can be a denaturant or temperature.

Vibrational circular dichroism of proteins

The more recent developments of vibrational circular dichroism (VCD) techniques for proteins, currently involving Fourier transform (FFT) instruments, provide powerful means for determining protein conformations in solution even for very large protein molecules. Such VCD studies of proteins are often combined with X-ray diffraction of protein crystals, FT-IR data for protein solutions in heavy water (D_2O), or *ab initio* quantum computations to provide unambiguous structural assignments that are unobtainable from CD.

Modern studies of folding with high time resolution

The study of protein folding has been greatly advanced in recent years by the development of fast, time-resolved techniques. These are experimental methods for rapidly triggering the folding of a sample of unfolded protein, and then observing the resulting dynamics. Fast techniques in widespread use include neutron scattering,^[23] ultrafast mixing of solutions, photochemical methods, and laser temperature jump spectroscopy. Among the many scientists who have contributed to the development of these techniques are Jeremy Cook, Heinrich Roder, Harry Gray, Martin Gruebele, Brian Dyer, William Eaton, Sheena Radford, Chris Dobson, Alan Fersht, Bengt Nölting and Lars Konermann.

Computational prediction of protein tertiary structure

De novo or *ab initio* techniques for computational protein structure prediction are related to, but strictly distinct from, studies involving protein folding. Molecular Dynamics (MD) is an important tool for studying protein folding and dynamics in silico. Because of computational cost, *ab initio* MD folding simulations with explicit water are limited to peptides and very small proteins.^{[24] [25]} MD simulations of larger proteins remain restricted to dynamics of the experimental structure or its high-temperature unfolding. In order to simulate long time folding processes (beyond about 1 microsecond), like folding of small-size proteins (about 50 residues) or larger, some approximations or simplifications in protein models need to be introduced. An approach using reduced protein representation (pseudo-atoms representing groups of atoms are defined) and statistical potential is not only useful in protein structure prediction, but is also capable of reproducing the folding pathways.^[26]

There are distributed computing projects which use idle CPU or GPU time of personal computers to solve problems such as protein folding or prediction of protein structure. People can run these programs on their computer or PlayStation 3 to support them. See links below (for example Folding@Home) to get information about how to participate in these projects.

Experimental techniques of protein structure determination

Folded structures of proteins are routinely determined by X-ray crystallography and NMR. Dynamic methods to characterise protein folding such as dual polarisation interferometry and CD provide a measurement of conformation and conformational change rather than structure.

See also

- Chevron plot
- Denaturation (biochemistry)
- Denaturation midpoint
- Downhill folding
- Folding (chemistry)
- Folding@Home
- Foldit computer game
- Levinthal paradox
- Protein design
- Protein dynamics
- Protein Misfolding Cyclic Amplification
- Protein structure prediction
- Protein structure prediction software
- Rosetta@home
- Software for molecular mechanics modeling

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External links

- FoldIt - Folding Protein Game (<http://fold.it/portal/info/science>)
- Folding@Home (<http://www.stanford.edu/group/pandegroup/folding/about.html>)
- Rosetta@Home (<http://boinc.bakerlab.org/rosetta>)

Protein domain

A **protein domain** is a part of protein sequence and structure that can evolve, function, and exist independently of the rest of the protein chain. Each domain forms a compact three-dimensional structure and often can be independently stable and folded. Many proteins consist of several structural domains. One domain may appear in a variety of different proteins. Molecular evolution uses domains as building blocks and these may be recombined in different arrangements to create proteins with different functions. Domains vary in length from between about 25 amino acids up to 500 amino acids in length. The shortest domains such as zinc fingers are stabilized by metal ions or disulfide bridges. Domains often form functional units, such as the calcium-binding EF hand domain of calmodulin. Because they are independently stable, domains can be "swapped" by genetic engineering between one protein and another to make chimeric proteins.

Background

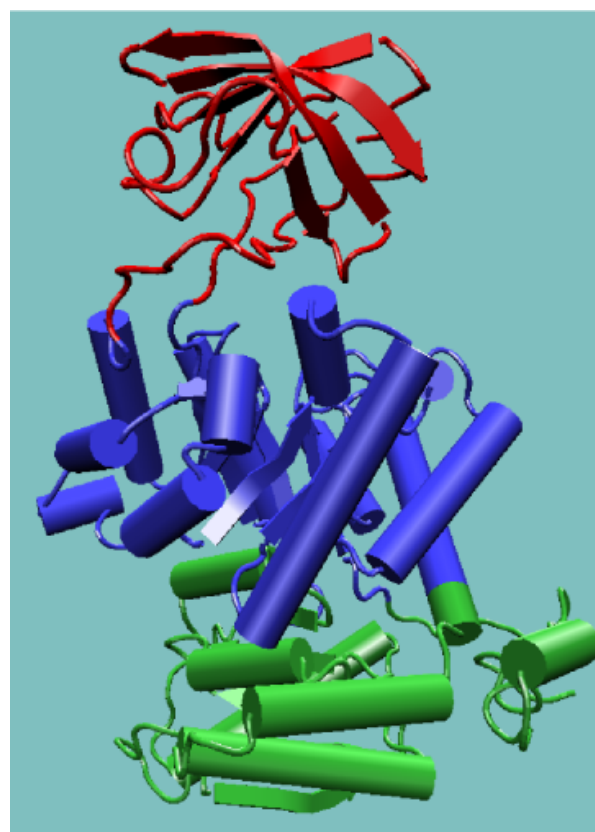
The concept of the **domain** was first proposed in 1973 by Wetlaufer after X-ray crystallographic studies of hen lysozyme ^[2] and papain ^[3] and by limited proteolysis studies of immunoglobulins ^[4] ^[5]. Wetlaufer defined domains as stable units of protein structure that could fold autonomously. In the past domains have been described as units of:

- compact structure^[6]
- function and evolution^[7]
- folding^[8].

Each definition is valid and will often overlap, i.e. a compact structural domain that is found amongst diverse proteins is likely to fold independently within its structural environment. Nature often brings several domains together to form multidomain and multifunctional proteins with a vast number of possibilities ^[9]. In a multidomain protein, each domain may fulfil its own function independently, or in a concerted manner with its neighbours. Domains can either serve as modules for building up large assemblies such as virus particles or muscle fibres, or can provide specific catalytic or binding sites as found in enzymes or regulatory proteins.

An appropriate example is pyruvate kinase, a glycolytic enzyme that plays an important role in regulating the flux from fructose-1,6-biphosphate to pyruvate. It contains an all- β regulatory domain, an α/β -substrate binding domain and an α/β -nucleotide binding domain, connected by several polypeptide linkers ^[10] (see figure, right). Each domain in this protein occurs in diverse sets of protein families.

The central α/β -barrel substrate binding domain is one of the most common enzyme folds. It is seen in many different enzyme families catalysing completely unrelated reactions ^[11]. The α/β -barrel is commonly called the TIM barrel named after triose phosphate isomerase, which was the first such structure to be solved ^[12]. It is currently classified into 26 homologous families in the CATH domain database ^[13]. The TIM barrel is formed from a



Pyruvate kinase, a protein from three domains (PDB 1pkn ^[1])

sequence of β - α - β motifs closed by the first and last strand hydrogen bonding together, forming an eight stranded barrel. There is debate about the evolutionary origin of this domain. One study has suggested that a single ancestral enzyme could have diverged into several families^[14], while another suggests that a stable TIM-barrel structure has evolved through convergent evolution^[15].

The TIM-barrel in pyruvate kinase is 'discontinuous', meaning that more than one segment of the polypeptide is required to form the domain. This is likely to be the result of the insertion of one domain into another during the protein's evolution. It has been shown from known structures that about a quarter of structural domains are discontinuous.^[16] ^[17] The inserted β -barrel regulatory domain is 'continuous', made up of a single stretch of polypeptide.

Covalent association of two domains represents a functional and structural advantage since there is an increase in stability when compared with the same structures non-covalently associated^[18]. Other, advantages are the protection of intermediates within inter-domain enzymatic clefts that may otherwise be unstable in aqueous environments, and a fixed stoichiometric ratio of the enzymatic activity necessary for a sequential set of reactions^[19].

Domains are units of protein structure

The primary structure (string of amino acids) of a protein ultimately encodes its uniquely folded 3D conformation.^[20] The most important factor governing the folding of a protein into 3D structure is the distribution of polar and non-polar side chains.^[21] Folding is driven by the burial of hydrophobic side chains into the interior of the molecule so to avoid contact with the aqueous environment. Generally proteins have a core of hydrophobic residues surrounded by a shell of hydrophilic residues. Since the peptide bonds themselves are polar they are neutralised by hydrogen bonding with each other when in the hydrophobic environment. This gives rise to regions of the polypeptide that form regular 3D structural patterns called secondary structure. There are two main types of secondary structure: α -helices and β -sheets.

Some simple combinations of secondary structure elements have been found to frequently occur in protein structure and are referred to as supersecondary structure or motifs. For example, the β -hairpin motif consists of two adjacent antiparallel β -strands joined by a small loop. It is present in most antiparallel β structures both as an isolated ribbon and as part of more complex β -sheets. Another common super-secondary structure is the β - α - β motif, which is frequently used to connect two parallel β -strands. The central α -helix connects the C-termini of the first strand to the N-termini of the second strand, packing its side chains against the β -sheet and therefore shielding the hydrophobic residues of the β -strands from the surface.

Structural alignment is an important tool for determining domains.

Tertiary structure of domains

Several motifs pack together to form compact, local, semi-independent units called domains.^[6] The overall 3D structure of the polypeptide chain is referred to as the protein's tertiary structure. Domains are the fundamental units of tertiary structure, each domain containing an individual hydrophobic core built from secondary structural units connected by loop regions. The packing of the polypeptide is usually much tighter in the interior than the exterior of the domain producing a solid-like core and a fluid-like surface.^[22] In fact, core residues are often conserved in a protein family, whereas the residues in loops are less conserved, unless they are involved in the protein's function. Protein tertiary structure can be divided into four main classes based on the secondary structural content of the domain.^[23]

- All- α domains have a domain core built exclusively from α -helices. This class is dominated by small folds, many of which form a simple bundle with helices running up and down.

- All- β domains have a core comprising of antiparallel β -sheets, usually two sheets packed against each other. Various patterns can be identified in the arrangement of the strands, often giving rise to the identification of recurring motifs, for example the Greek key motif.^[24]
- α + β domains are a mixture of all- α and all- β motifs. Classification of proteins into this class is difficult because of overlaps to the other three classes and therefore is not used in the CATH domain database.^[13]
- α/β domains are made from a combination of β - α - β motifs that predominantly form a parallel β -sheet surrounded by amphipathic α -helices. The secondary structures are arranged in layers or barrels.

Domains have limits on size

Domains have limits on size.^[25] The size of individual structural domains varies from 36 residues in E-selectin to 692 residues in lipoxygenase-1,^[16] but the majority, 90%, have less than 200 residues^[26] with an average of approximately 100 residues.^[27] Very short domains, less than 40 residues, are often stabilised by metal ions or disulfide bonds. Larger domains, greater than 300 residues, are likely to consist of multiple hydrophobic cores.^[28]

Domains and quaternary structure

Many proteins have a quaternary structure, which consists of several polypeptide chains that associate into an oligomeric molecule. Each polypeptide chain in such a protein is called a subunit. Hemoglobin, for example, consists of two α and two β subunits. Each of the four chains has an all- α globin fold with a heme pocket.

Domain swapping is a mechanism for forming oligomeric assemblies.^[29] In domain swapping, a secondary or tertiary element of a monomeric protein is replaced by the same element of another protein. Domain swapping can range from secondary structure elements to whole structural domains. It also represents a model of evolution for functional adaptation by oligomerisation, e.g. oligomeric enzymes that have their active site at subunit interfaces.^[30]

Domains as evolutionary modules

Nature is a tinkerer and not an inventor,^[31] new sequences are adapted from pre-existing sequences rather than invented. Domains are the common material used by nature to generate new sequences, they can be thought of as genetically mobile units, referred to as 'modules'. Often, the C and N termini of domains are close together in space, allowing them to easily be "slotted into" parent structures during the process of evolution. Many domain families are found in all three forms of life, Archaea, Bacteria and Eukarya. Domains that are repeatedly found in diverse proteins are often referred to as modules, examples can be found among extracellular proteins associated with clotting, fibrinolysis, complement, the extracellular matrix, cell surface adhesion molecules and cytokine receptors.^[32]

Molecular evolution gives rise to families of related proteins with similar sequence and structure. However, sequence similarities can be extremely low between proteins that share the same structure. Protein structures may be similar because proteins have diverged from a common ancestor. Alternatively, some folds may be more favored than others as they represent stable arrangements of secondary structures and some proteins may converge towards these folds over the course of evolution. There are currently about 45,000 experimentally determined protein 3D structures deposited within the Protein Data Bank (PDB).^[33] However this set contains a lot of identical or very similar structures. All proteins should be classified to structural families to understand their evolutionary relationships. Structural comparisons are best achieved at the domain level. For this reason many algorithms have been developed to automatically assign domains in proteins with known 3D structure, see 'Domain definition from structural co-ordinates'.

The CATH domain database classifies domains into approximately 800 fold families, ten of these folds are highly populated and are referred to as 'super-folds'. Super-folds are defined as folds for which there are at least three structures without significant sequence similarity.^[34] The most populated is the α/β -barrel super-fold as described previously.

Multidomain proteins

The majority of genomic proteins, two-thirds in unicellular organisms and more than 80% in metazoa, are multidomain proteins created as a result of gene duplication events.^[35] Many domains in multidomain structures could have once existed as independent proteins. More and more domains in eukaryotic multidomain proteins can be found as independent proteins in prokaryotes.^[36] For example, vertebrates have a multi-enzyme polypeptide containing the GAR synthetase, AIR synthetase and GAR transformylase modules (GARs-AIRs-GARt; GAR: glycylamide ribonucleotide synthetase/transferase; AIR: aminoimidazole ribonucleotide synthetase). In insects, the polypeptide appears as GARs-(AIRs)₂-GARt, in yeast GARs-AIRs is encoded separately from GARt, and in bacteria each domain is encoded separately.^[37]

Origin

Multidomain proteins are likely to have emerged from a selective pressure during evolution to create new functions. Various proteins have diverged from common ancestors by different combinations and associations of domains. Modular units frequently move about, within and between biological systems through mechanisms of genetic shuffling:

- transposition of mobile elements including horizontal transfers (between species),^[38]
- gross rearrangements such as inversions, translocations, deletions and duplications;
- homologous recombination;
- slippage of DNA polymerase during replication.

Types of organisation

The simplest multidomain organisation seen in proteins is that of a single domain repeated in tandem.^[39] The domains may interact with each other or remain isolated, like beads on string. The giant 30,000 residue muscle protein titin comprises about 120 fibronectin-III-type and Ig-type domains.^[40] In the serine proteases, a gene duplication event has led to the formation of a two β -barrel domain enzyme.^[41] The repeats have diverged so widely that there is no obvious sequence similarity between them. The active site is located at a cleft between the two β -barrel domains, in which functionally important residues are contributed from each domain. Genetically engineered mutants of the chymotrypsin serine protease were shown to have some proteinase activity even though their active site residues were abolished and it has therefore been postulated that the duplication event enhanced the enzyme's activity.^[41]

Modules frequently display different connectivity relationships, as illustrated by the kinesins and ABC transporters. The kinesin motor domain can be at either end of a polypeptide chain that includes a coiled-coil region and a cargo domain.^[42] ABC transporters are built with up to four domains consisting of two unrelated modules, ATP-binding cassette and an integral membrane module, arranged in various combinations.

Not only do domains recombine, but there are many examples of a domain having been inserted into another. Sequence or structural similarities to other domains demonstrate that homologues of inserted and parent domains can exist independently. An example is that of the 'fingers' inserted into the 'palm' domain within the polymerases of the Pol I family.^[43] Since a domain can be inserted into another, there should always be at least one continuous domain in a multidomain protein. This is the main difference between definitions of structural domains and evolutionary/functional domains. An evolutionary domain will be limited to one or two connections between domains, whereas structural domains can have unlimited connections, within a given criterion of the existence of a common core. Several structural domains could be assigned to an evolutionary domain.

Domains are autonomous folding units

Folding

Protein folding - the unsolved problem : Since the seminal work of Anfinsen over forty years ago,^[20] the goal to completely understand the mechanism by which a polypeptide rapidly folds into its stable native conformation remains elusive. Many experimental folding studies have contributed much to our understanding, but the principles that govern protein folding are still based on those discovered in the very first studies of folding. Anfinsen showed that the native state of a protein is thermodynamically stable, the conformation being at a global minimum of its free energy.

Folding is a directed search of conformational space allowing the protein to fold on a biologically feasible time scale. The Levinthal paradox states that if an averaged sized protein would sample all possible conformations before finding the one with the lowest energy, the whole process would take billions of years.^[44] Proteins typically fold within 0.1 and 1000 seconds, therefore the protein folding process must be directed some way through a specific folding pathway. The forces that direct this search are likely to be a combination of local and global influences whose effects are felt at various stages of the reaction.^[45]

Advances in experimental and theoretical studies have shown that folding can be viewed in terms of energy landscapes,^{[46] [47]} where folding kinetics is considered as a progressive organisation of an ensemble of partially folded structures through which a protein passes on its way to the folded structure. This has been described in terms of a folding funnel, in which an unfolded protein has a large number of conformational states available and there are fewer states available to the folded protein. A funnel implies that for protein folding there is a decrease in energy and loss of entropy with increasing tertiary structure formation. The local roughness of the funnel reflects kinetic traps, corresponding to the accumulation of misfolded intermediates. A folding chain progresses toward lower intra-chain free-energies by increasing its compactness. The chains conformational options become increasingly narrowed ultimately toward one native structure.

Advantage of domains in protein folding

The organisation of large proteins by structural domains represents an advantage for protein folding, with each domain being able to individually fold, accelerating the folding process and reducing a potentially large combination of residue interactions. Furthermore, given the observed random distribution of hydrophobic residues in proteins,^[48] domain formation appears to be the optimal solution for a large protein to bury its hydrophobic residues while keeping the hydrophilic residues at the surface.^{[49] [50]}

However, the role of inter-domain interactions in protein folding and in energetics of stabilisation of the native structure, probably differs for each protein. In T4 lysozyme, the influence of one domain on the other is so strong that the entire molecule is resistant to proteolytic cleavage. In this case, folding is a sequential process where the C-terminal domain is required to fold independently in an early step, and the other domain requires the presence of the folded C-terminal domain for folding and stabilisation.^[51]

It has been found that the folding of an isolated domain can take place at the same rate or sometimes faster than that of the integrated domain.^[52] Suggesting that unfavourable interactions with the rest of the protein can occur during folding. Several arguments suggest that the slowest step in the folding of large proteins is the pairing of the folded domains.^[28] This is either because the domains are not folded entirely correctly or because the small adjustments required for their interaction are energetically unfavourable,^[53] such as the removal of water from the domain interface.

Domains and protein flexibility

The presence of multiple domains in proteins gives rise to a great deal of flexibility and mobility, leading to **protein domain dynamics**. Domain motions can be inferred by comparing different structures of a protein, or they can be directly observed using spectra^[54] ^[55] measured by neutron spin echo spectroscopy. They can also be suggested by sampling in extensive molecular dynamics trajectories^[56]. Domain motions are important for:^[57]

- catalysis;
- regulatory activity;
- transport of metabolites;
- formation of protein assemblies; and
- cellular locomotion.

One of the largest observed domain motions is the 'swivelling' mechanism in pyruvate phosphate dikinase. The phosphoinositide domain swivels between two states in order to bring a phosphate group from the active site of the nucleotide binding domain to that of the phosphoenolpyruvate/pyruvate domain.^[58] The phosphate group is moved over a distance of 45Å involving a domain motion of about 100 degrees around a single residue. In enzymes, the closure of one domain onto another captures a substrate by an induced fit, allowing the reaction to take place in a controlled way. A detailed analysis by Gerstein led to the classification of two basic types of domain motion; hinge and shear.^[57] Only a relatively small portion of the chain, namely the inter-domain linker and side chains undergo significant conformational changes upon domain rearrangement.^[59]

Hinges by secondary structures

A study by Hayward^[60] found that the termini of α -helices and β -sheets form hinges in a large number of cases. Many hinges were found to involve two secondary structure elements acting like hinges of a door, allowing an opening and closing motion to occur. This can arise when two neighbouring strands within a β -sheet situated in one domain, diverge apart as they join the other domain. The two resulting termini then form the bending regions between the two domains. α -helices that preserve their hydrogen bonding network when bent are found to behave as mechanical hinges, storing 'elastic energy' that drives the closure of domains for rapid capture of a substrate.^[60]

Helical to extended conformation

The interconversion of helical and extended conformations at the site of a domain boundary is not uncommon. In calmodulin, torsion angles change for five residues in the middle of a domain linking α -helix. The helix is split into two, almost perpendicular, smaller helices separated by four residues of an extended strand.^[61] ^[62]

Shear motions

Shear motions involve a small sliding movement of domain interfaces, controlled by the amino acid side chains within the interface. Proteins displaying shear motions often have a layered architecture: stacking of secondary structures. The interdomain linker has merely the role of keeping the domains in close proximity.

Domain motion and functional dynamics in enzymes

The analysis of the internal dynamics of structurally different, but functionally similar enzymes has highlighted a common relationship between the positioning of the active site and the two principal protein sub-domains. In fact, for several members of the hydrolase superfamily, the catalytic site is located close to the interface separating the two principal quasi-rigid domains^[56]. Such positioning appears instrumental for maintaining the precise geometry of the active site, while allowing for an appreciable functionally-oriented modulation of the flanking regions resulting from the relative motion of the two sub-domains.

Domain definition from structural co-ordinates

The importance of domains as structural building blocks and elements of evolution has brought about many automated methods for their identification and classification in proteins of known structure. Automatic procedures for reliable domain assignment is essential for the generation of the domain databases, especially as the number of protein structures is increasing. Although the boundaries of a domain can be determined by visual inspection, construction of an automated method is not straightforward. Problems occur when faced with domains that are discontinuous or highly associated.^[63] The fact that there is no standard definition of what a domain really is has meant that domain assignments have varied enormously, with each researcher using a unique set of criteria.^[64]

A structural domain is a compact, globular sub-structure with more interactions within it than with the rest of the protein.^[59] Therefore, a structural domain can be determined by two visual characteristics; its compactness and its extent of isolation.^[65] Measures of local compactness in proteins have been used in many of the early methods of domain assignment^{[66] [67] [68] [69]} and in several of the more recent methods.^{[26] [70] [71] [72] [73]}

Methods

One of the first algorithms^[66] used a C α -C α distance map together with a hierarchical clustering routine that considered proteins as several small segments, 10 residues in length. The initial segments were clustered one after another based on inter-segment distances; segments with the shortest distances were clustered and considered as single segments thereafter. The stepwise clustering finally included the full protein. Go^[69] also exploited the fact that inter-domain distances are normally larger than intra-domain distances; all possible C α -C α distances were represented as diagonal plots in which there were distinct patterns for helices, extended strands and combinations of secondary structures.

The method by Sowdhamini and Blundell clusters secondary structures in a protein based on their C α -C α distances and identifies domains from the pattern in their dendrograms.^[63] As the procedure does not consider the protein as a continuous chain of amino acids there are no problems in treating discontinuous domains. Specific nodes in these dendrograms are identified as tertiary structural clusters of the protein, these include both super-secondary structures and domains. The DOMAK algorithm is used to create the 3Dee domain database.^[71] It calculates a 'split value' from the number of each type of contact when the protein is divided arbitrarily into two parts. This split value is large when the two parts of the structure are distinct.

The method of Wodak and Janin^[74] was based on the calculated interface areas between two chain segments repeatedly cleaved at various residue positions. Interface areas were calculated by comparing surface areas of the cleaved segments with that of the native structure. Potential domain boundaries can be identified at a site where the interface area was at a minimum. Other methods have used measures of solvent accessibility to calculate compactness.^{[26] [75] [76]}

The PUU algorithm^[17] incorporates a harmonic model used to approximate inter-domain dynamics. The underlying physical concept is that many rigid interactions will occur within each domain and loose interactions will occur between domains. This algorithm is used to define domains in the FSSP domain database.^[70]

Swindells (1995) developed a method, DETECTIVE, for identification of domains in protein structures based on the idea that domains have a hydrophobic interior. Deficiencies were found to occur when hydrophobic cores from different domains continue through the interface region.

RigidFinder^[77] is a novel method for identification of protein rigid blocks (domains and loops) from two different conformations. Rigid blocks are defined as blocks where all inter residue distances are conserved across conformations.

A general method to identify *dynamical domains*, that is protein regions that behave approximately as rigid units in the course of structural fluctuations, has been introduced by Potestio et al.^[56] and, among other applications was also used to compare the consistency of the dynamics-based domain subdivisions with standard structure-based ones. The

method, termed PiSQRD^[78], is publicly available in the form of a webserver^[79]. The latter allows users to optimally subdivide single-chain or multimeric proteins into quasi-rigid domains^[56] ^[79] based on the collective modes of fluctuation of the system. By default the latter are calculated through an elastic network model^[80]; alternatively pre-calculated essential dynamical spaces can be uploaded by the user.

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External links

- The Protein Families (Pfam) database clan browser (<http://www.sanger.ac.uk//Software/Pfam/browse/clans.shtml#159>) provides easy access to information about protein structural domains. A clan contains two or more **Pfam** families that have arisen from a single evolutionary origin.

Structural domain databases

- Conserved Domains at the National Center for Biotechnology website (<http://www.ncbi.nlm.nih.gov/books/bv.fcgi?call=bv.View..ShowSection&rid=handbook.section.110>)
- 3Dee (<http://www.compbio.dundee.ac.uk/3Dee/>)
- CATH (<http://www.cathdb.info/>)
- DALI (http://ekhidna.biocenter.helsinki.fi/dali_server/)
- SCOP (<http://scop.mrc-lmb.cam.ac.uk/scop>)
- Pawson Lab - Protein interaction domains (http://pawsonlab.mshri.on.ca/index.php?option=com_content&task=view&id=30&Itemid=63/)
- Nash Lab - Protein interaction domains in Signal Transduction (http://nashlab.bsd.uchicago.edu/index.php?option=com_content&task=section&id=4&Itemid=29)
- Definition and assignment of structural domains in proteins (<http://realm.sdsc.edu/pdomains/>).

Sequence domain databases

- InterPro (<http://www.ebi.ac.uk/interpro>)
- Pfam (<http://pfam.sanger.ac.uk/>)
- PROSITE (<http://www.expasy.org/prosite/>)
- ProDom (<http://prodom.prabi.fr>)
- SMART (<http://SMART.embl-heidelberg.de>)
- NCBI Conserved Domain Database (<http://www.ncbi.nlm.nih.gov:80/Structure/cdd/cdd.shtml>)
- SUPERFAMILY (<http://supfam.org/SUPERFAMILY>) Library of HMMs representing superfamilies and database of (superfamily and family) annotations for all completely sequenced organisms

Protein dynamics

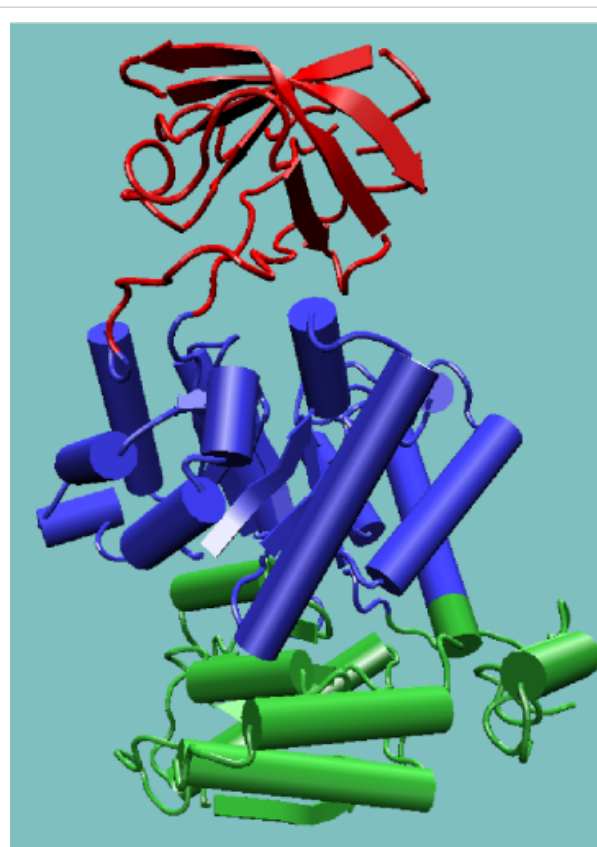
A **protein domain** is a part of protein sequence and structure that can evolve, function, and exist independently of the rest of the protein chain. Each domain forms a compact three-dimensional structure and often can be independently stable and folded. Many proteins consist of several structural domains. One domain may appear in a variety of different proteins. Molecular evolution uses domains as building blocks and these may be recombined in different arrangements to create proteins with different functions. Domains vary in length from between about 25 amino acids up to 500 amino acids in length. The shortest domains such as zinc fingers are stabilized by metal ions or disulfide bridges. Domains often form functional units, such as the calcium-binding EF hand domain of calmodulin. Because they are independently stable, domains can be "swapped" by genetic engineering between one protein and another to make chimeric proteins.

Background

The concept of the **domain** was first proposed in 1973 by Wetlaufer after X-ray crystallographic studies of hen lysozyme ^[1] and papain ^[2] and by limited proteolysis studies of immunoglobulins ^[3] ^[4]. Wetlaufer defined domains as stable units of protein structure that could fold autonomously. In the past domains have been described as units of:

- compact structure^[5]
- function and evolution^[6]
- folding ^[7].

Each definition is valid and will often overlap, i.e. a compact structural domain that is found amongst diverse proteins is likely to fold independently within its structural environment. Nature often brings several domains together to form multidomain and multifunctional proteins with a vast number of possibilities ^[8]. In a multidomain protein, each domain may fulfil its own function independently, or in a concerted manner with its neighbours.



Pyruvate kinase, a protein from three domains (PDB 1pkn ^[1])

Domains can either serve as modules for building up large assemblies such as virus particles or muscle fibres, or can provide specific catalytic or binding sites as found in enzymes or regulatory proteins.

An appropriate example is pyruvate kinase, a glycolytic enzyme that plays an important role in regulating the flux from fructose-1,6-biphosphate to pyruvate. It contains an all- β regulatory domain, an α/β -substrate binding domain and an α/β -nucleotide binding domain, connected by several polypeptide linkers^[9] (see figure, right). Each domain in this protein occurs in diverse sets of protein families.

The central α/β -barrel substrate binding domain is one of the most common enzyme folds. It is seen in many different enzyme families catalysing completely unrelated reactions^[10]. The α/β -barrel is commonly called the TIM barrel named after triose phosphate isomerase, which was the first such structure to be solved^[11]. It is currently classified into 26 homologous families in the CATH domain database^[12]. The TIM barrel is formed from a sequence of β - α - β motifs closed by the first and last strand hydrogen bonding together, forming an eight stranded barrel. There is debate about the evolutionary origin of this domain. One study has suggested that a single ancestral enzyme could have diverged into several families^[13], while another suggests that a stable TIM-barrel structure has evolved through convergent evolution^[14].

The TIM-barrel in pyruvate kinase is 'discontinuous', meaning that more than one segment of the polypeptide is required to form the domain. This is likely to be the result of the insertion of one domain into another during the protein's evolution. It has been shown from known structures that about a quarter of structural domains are discontinuous.^{[15] [16]} The inserted β -barrel regulatory domain is 'continuous', made up of a single stretch of polypeptide.

Covalent association of two domains represents a functional and structural advantage since there is an increase in stability when compared with the same structures non-covalently associated^[17]. Other, advantages are the protection of intermediates within inter-domain enzymatic clefts that may otherwise be unstable in aqueous environments, and a fixed stoichiometric ratio of the enzymatic activity necessary for a sequential set of reactions^[18].

Domains are units of protein structure

The primary structure (string of amino acids) of a protein ultimately encodes its uniquely folded 3D conformation.^[19] The most important factor governing the folding of a protein into 3D structure is the distribution of polar and non-polar side chains.^[20] Folding is driven by the burial of hydrophobic side chains into the interior of the molecule so to avoid contact with the aqueous environment. Generally proteins have a core of hydrophobic residues surrounded by a shell of hydrophilic residues. Since the peptide bonds themselves are polar they are neutralised by hydrogen bonding with each other when in the hydrophobic environment. This gives rise to regions of the polypeptide that form regular 3D structural patterns called secondary structure. There are two main types of secondary structure: α -helices and β -sheets.

Some simple combinations of secondary structure elements have been found to frequently occur in protein structure and are referred to as supersecondary structure or motifs. For example, the β -hairpin motif consists of two adjacent antiparallel β -strands joined by a small loop. It is present in most antiparallel β structures both as an isolated ribbon and as part of more complex β -sheets. Another common super-secondary structure is the β - α - β motif, which is frequently used to connect two parallel β -strands. The central α -helix connects the C-termini of the first strand to the N-termini of the second strand, packing its side chains against the β -sheet and therefore shielding the hydrophobic residues of the β -strands from the surface.

Structural alignment is an important tool for determining domains.

Tertiary structure of domains

Several motifs pack together to form compact, local, semi-independent units called domains.^[5] The overall 3D structure of the polypeptide chain is referred to as the protein's tertiary structure. Domains are the fundamental units of tertiary structure, each domain containing an individual hydrophobic core built from secondary structural units connected by loop regions. The packing of the polypeptide is usually much tighter in the interior than the exterior of the domain producing a solid-like core and a fluid-like surface.^[21] In fact, core residues are often conserved in a protein family, whereas the residues in loops are less conserved, unless they are involved in the protein's function. Protein tertiary structure can be divided into four main classes based on the secondary structural content of the domain.^[22]

- All- α domains have a domain core built exclusively from α -helices. This class is dominated by small folds, many of which form a simple bundle with helices running up and down.
- All- β domains have a core comprising of antiparallel β -sheets, usually two sheets packed against each other. Various patterns can be identified in the arrangement of the strands, often giving rise to the identification of recurring motifs, for example the Greek key motif.^[23]
- α + β domains are a mixture of all- α and all- β motifs. Classification of proteins into this class is difficult because of overlaps to the other three classes and therefore is not used in the CATH domain database.^[12]
- α / β domains are made from a combination of β - α - β motifs that predominantly form a parallel β -sheet surrounded by amphipathic α -helices. The secondary structures are arranged in layers or barrels.

Domains have limits on size

Domains have limits on size.^[24] The size of individual structural domains varies from 36 residues in E-selectin to 692 residues in lipoxygenase-1,^[15] but the majority, 90%, have less than 200 residues^[25] with an average of approximately 100 residues.^[26] Very short domains, less than 40 residues, are often stabilised by metal ions or disulfide bonds. Larger domains, greater than 300 residues, are likely to consist of multiple hydrophobic cores.^[27]

Domains and quaternary structure

Many proteins have a quaternary structure, which consists of several polypeptide chains that associate into an oligomeric molecule. Each polypeptide chain in such a protein is called a subunit. Hemoglobin, for example, consists of two α and two β subunits. Each of the four chains has an all- α globin fold with a heme pocket.

Domain swapping is a mechanism for forming oligomeric assemblies.^[28] In domain swapping, a secondary or tertiary element of a monomeric protein is replaced by the same element of another protein. Domain swapping can range from secondary structure elements to whole structural domains. It also represents a model of evolution for functional adaptation by oligomerisation, e.g. oligomeric enzymes that have their active site at subunit interfaces.^[29]

Domains as evolutionary modules

Nature is a tinkerer and not an inventor,^[30] new sequences are adapted from pre-existing sequences rather than invented. Domains are the common material used by nature to generate new sequences, they can be thought of as genetically mobile units, referred to as 'modules'. Often, the C and N termini of domains are close together in space, allowing them to easily be "slotted into" parent structures during the process of evolution. Many domain families are found in all three forms of life, Archaea, Bacteria and Eukarya. Domains that are repeatedly found in diverse proteins are often referred to as modules, examples can be found among extracellular proteins associated with clotting, fibrinolysis, complement, the extracellular matrix, cell surface adhesion molecules and cytokine receptors.^[31]

Molecular evolution gives rise to families of related proteins with similar sequence and structure. However, sequence similarities can be extremely low between proteins that share the same structure. Protein structures may be similar

because proteins have diverged from a common ancestor. Alternatively, some folds may be more favored than others as they represent stable arrangements of secondary structures and some proteins may converge towards these folds over the course of evolution. There are currently about 45,000 experimentally determined protein 3D structures deposited within the Protein Data Bank (PDB).^[32] However this set contains a lot of identical or very similar structures. All proteins should be classified to structural families to understand their evolutionary relationships. Structural comparisons are best achieved at the domain level. For this reason many algorithms have been developed to automatically assign domains in proteins with known 3D structure, see 'Domain definition from structural co-ordinates'.

The CATH domain database classifies domains into approximately 800 fold families, ten of these folds are highly populated and are referred to as 'super-folds'. Super-folds are defined as folds for which there are at least three structures without significant sequence similarity.^[33] The most populated is the α/β -barrel super-fold as described previously.

Multidomain proteins

The majority of genomic proteins, two-thirds in unicellular organisms and more than 80% in metazoa, are multidomain proteins created as a result of gene duplication events.^[34] Many domains in multidomain structures could have once existed as independent proteins. More and more domains in eukaryotic multidomain proteins can be found as independent proteins in prokaryotes.^[35] For example, vertebrates have a multi-enzyme polypeptide containing the GAR synthetase, AIR synthetase and GAR transformylase modules (GARs-AIRs-GARt; GAR: glycylamide ribonucleotide synthetase/transferase; AIR: aminoimidazole ribonucleotide synthetase). In insects, the polypeptide appears as GARs-(AIRs)₂-GARt, in yeast GARs-AIRs is encoded separately from GARt, and in bacteria each domain is encoded separately.^[36]

Origin

Multidomain proteins are likely to have emerged from a selective pressure during evolution to create new functions. Various proteins have diverged from common ancestors by different combinations and associations of domains. Modular units frequently move about, within and between biological systems through mechanisms of genetic shuffling:

- transposition of mobile elements including horizontal transfers (between species),^[37]
- gross rearrangements such as inversions, translocations, deletions and duplications;
- homologous recombination;
- slippage of DNA polymerase during replication.

Types of organisation

The simplest multidomain organisation seen in proteins is that of a single domain repeated in tandem.^[38] The domains may interact with each other or remain isolated, like beads on string. The giant 30,000 residue muscle protein titin comprises about 120 fibronectin-III-type and Ig-type domains.^[39] In the serine proteases, a gene duplication event has led to the formation of a two β -barrel domain enzyme.^[40] The repeats have diverged so widely that there is no obvious sequence similarity between them. The active site is located at a cleft between the two β -barrel domains, in which functionally important residues are contributed from each domain. Genetically engineered mutants of the chymotrypsin serine protease were shown to have some proteinase activity even though their active site residues were abolished and it has therefore been postulated that the duplication event enhanced the enzyme's activity.^[40]

Modules frequently display different connectivity relationships, as illustrated by the kinesins and ABC transporters. The kinesin motor domain can be at either end of a polypeptide chain that includes a coiled-coil region and a cargo domain.^[41] ABC transporters are built with up to four domains consisting of two unrelated modules, ATP-binding

cassette and an integral membrane module, arranged in various combinations.

Not only do domains recombine, but there are many examples of a domain having been inserted into another. Sequence or structural similarities to other domains demonstrate that homologues of inserted and parent domains can exist independently. An example is that of the 'fingers' inserted into the 'palm' domain within the polymerases of the Pol I family.^[42] Since a domain can be inserted into another, there should always be at least one continuous domain in a multidomain protein. This is the main difference between definitions of structural domains and evolutionary/functional domains. An evolutionary domain will be limited to one or two connections between domains, whereas structural domains can have unlimited connections, within a given criterion of the existence of a common core. Several structural domains could be assigned to an evolutionary domain.

Domains are autonomous folding units

Folding

Protein folding - the unsolved problem : Since the seminal work of Anfinsen over forty years ago,^[19] the goal to completely understand the mechanism by which a polypeptide rapidly folds into its stable native conformation remains elusive. Many experimental folding studies have contributed much to our understanding, but the principles that govern protein folding are still based on those discovered in the very first studies of folding. Anfinsen showed that the native state of a protein is thermodynamically stable, the conformation being at a global minimum of its free energy.

Folding is a directed search of conformational space allowing the protein to fold on a biologically feasible time scale. The Levinthal paradox states that if an averaged sized protein would sample all possible conformations before finding the one with the lowest energy, the whole process would take billions of years.^[43] Proteins typically fold within 0.1 and 1000 seconds, therefore the protein folding process must be directed some way through a specific folding pathway. The forces that direct this search are likely to be a combination of local and global influences whose effects are felt at various stages of the reaction.^[44]

Advances in experimental and theoretical studies have shown that folding can be viewed in terms of energy landscapes,^{[45] [46]} where folding kinetics is considered as a progressive organisation of an ensemble of partially folded structures through which a protein passes on its way to the folded structure. This has been described in terms of a folding funnel, in which an unfolded protein has a large number of conformational states available and there are fewer states available to the folded protein. A funnel implies that for protein folding there is a decrease in energy and loss of entropy with increasing tertiary structure formation. The local roughness of the funnel reflects kinetic traps, corresponding to the accumulation of misfolded intermediates. A folding chain progresses toward lower intra-chain free-energies by increasing its compactness. The chains conformational options become increasingly narrowed ultimately toward one native structure.

Advantage of domains in protein folding

The organisation of large proteins by structural domains represents an advantage for protein folding, with each domain being able to individually fold, accelerating the folding process and reducing a potentially large combination of residue interactions. Furthermore, given the observed random distribution of hydrophobic residues in proteins,^[47] domain formation appears to be the optimal solution for a large protein to bury its hydrophobic residues while keeping the hydrophilic residues at the surface.^{[48] [49]}

However, the role of inter-domain interactions in protein folding and in energetics of stabilisation of the native structure, probably differs for each protein. In T4 lysozyme, the influence of one domain on the other is so strong that the entire molecule is resistant to proteolytic cleavage. In this case, folding is a sequential process where the C-terminal domain is required to fold independently in an early step, and the other domain requires the presence of the folded C-terminal domain for folding and stabilisation.^[50]

It has been found that the folding of an isolated domain can take place at the same rate or sometimes faster than that of the integrated domain.^[51] Suggesting that unfavourable interactions with the rest of the protein can occur during folding. Several arguments suggest that the slowest step in the folding of large proteins is the pairing of the folded domains.^[27] This is either because the domains are not folded entirely correctly or because the small adjustments required for their interaction are energetically unfavourable,^[52] such as the removal of water from the domain interface.

Domains and protein flexibility

The presence of multiple domains in proteins gives rise to a great deal of flexibility and mobility, leading to **protein domain dynamics**. Domain motions can be inferred by comparing different structures of a protein, or they can be directly observed using spectra^[53] ^[54] measured by neutron spin echo spectroscopy. They can also be suggested by sampling in extensive molecular dynamics trajectories^[55]. Domain motions are important for:^[56]

- catalysis;
- regulatory activity;
- transport of metabolites;
- formation of protein assemblies; and
- cellular locomotion.

One of the largest observed domain motions is the 'swivelling' mechanism in pyruvate phosphate dikinase. The phosphoinositide domain swivels between two states in order to bring a phosphate group from the active site of the nucleotide binding domain to that of the phosphoenolpyruvate/pyruvate domain.^[57] The phosphate group is moved over a distance of 45Å involving a domain motion of about 100 degrees around a single residue. In enzymes, the closure of one domain onto another captures a substrate by an induced fit, allowing the reaction to take place in a controlled way. A detailed analysis by Gerstein led to the classification of two basic types of domain motion; hinge and shear.^[56] Only a relatively small portion of the chain, namely the inter-domain linker and side chains undergo significant conformational changes upon domain rearrangement.^[58]

Hinges by secondary structures

A study by Hayward^[59] found that the termini of α -helices and β -sheets form hinges in a large number of cases. Many hinges were found to involve two secondary structure elements acting like hinges of a door, allowing an opening and closing motion to occur. This can arise when two neighbouring strands within a β -sheet situated in one domain, diverge apart as they join the other domain. The two resulting termini then form the bending regions between the two domains. α -helices that preserve their hydrogen bonding network when bent are found to behave as mechanical hinges, storing 'elastic energy' that drives the closure of domains for rapid capture of a substrate.^[59]

Helical to extended conformation

The interconversion of helical and extended conformations at the site of a domain boundary is not uncommon. In calmodulin, torsion angles change for five residues in the middle of a domain linking α -helix. The helix is split into two, almost perpendicular, smaller helices separated by four residues of an extended strand.^[60] ^[61]

Shear motions

Shear motions involve a small sliding movement of domain interfaces, controlled by the amino acid side chains within the interface. Proteins displaying shear motions often have a layered architecture: stacking of secondary structures. The interdomain linker has merely the role of keeping the domains in close proximity.

Domain motion and functional dynamics in enzymes

The analysis of the internal dynamics of structurally different, but functionally similar enzymes has highlighted a common relationship between the positioning of the active site and the two principal protein sub-domains. In fact, for several members of the hydrolase superfamily, the catalytic site is located close to the interface separating the two principal quasi-rigid domains^[55]. Such positioning appears instrumental for maintaining the precise geometry of the active site, while allowing for an appreciable functionally-oriented modulation of the flanking regions resulting from the relative motion of the two sub-domains.

Domain definition from structural co-ordinates

The importance of domains as structural building blocks and elements of evolution has brought about many automated methods for their identification and classification in proteins of known structure. Automatic procedures for reliable domain assignment is essential for the generation of the domain databases, especially as the number of protein structures is increasing. Although the boundaries of a domain can be determined by visual inspection, construction of an automated method is not straightforward. Problems occur when faced with domains that are discontinuous or highly associated.^[62] The fact that there is no standard definition of what a domain really is has meant that domain assignments have varied enormously, with each researcher using a unique set of criteria.^[63]

A structural domain is a compact, globular sub-structure with more interactions within it than with the rest of the protein.^[58] Therefore, a structural domain can be determined by two visual characteristics; its compactness and its extent of isolation.^[64] Measures of local compactness in proteins have been used in many of the early methods of domain assignment^{[65] [66] [67] [68]} and in several of the more recent methods.^{[25] [69] [70] [71] [72]}

Methods

One of the first algorithms^[65] used a Ca-Ca distance map together with a hierarchical clustering routine that considered proteins as several small segments, 10 residues in length. The initial segments were clustered one after another based on inter-segment distances; segments with the shortest distances were clustered and considered as single segments thereafter. The stepwise clustering finally included the full protein. Go^[68] also exploited the fact that inter-domain distances are normally larger than intra-domain distances; all possible Ca-Ca distances were represented as diagonal plots in which there were distinct patterns for helices, extended strands and combinations of secondary structures.

The method by Sowdhamini and Blundell clusters secondary structures in a protein based on their Ca-Ca distances and identifies domains from the pattern in their dendrograms.^[62] As the procedure does not consider the protein as a continuous chain of amino acids there are no problems in treating discontinuous domains. Specific nodes in these dendrograms are identified as tertiary structural clusters of the protein, these include both super-secondary structures and domains. The DOMAK algorithm is used to create the 3Dee domain database.^[70] It calculates a 'split value' from the number of each type of contact when the protein is divided arbitrarily into two parts. This split value is large when the two parts of the structure are distinct.

The method of Wodak and Janin^[73] was based on the calculated interface areas between two chain segments repeatedly cleaved at various residue positions. Interface areas were calculated by comparing surface areas of the cleaved segments with that of the native structure. Potential domain boundaries can be identified at a site where the interface area was at a minimum. Other methods have used measures of solvent accessibility to calculate compactness.^{[25] [74] [75]}

The PUU algorithm^[16] incorporates a harmonic model used to approximate inter-domain dynamics. The underlying physical concept is that many rigid interactions will occur within each domain and loose interactions will occur between domains. This algorithm is used to define domains in the FSSP domain database.^[69]

Swindells (1995) developed a method, DETECTIVE, for identification of domains in protein structures based on the idea that domains have a hydrophobic interior. Deficiencies were found to occur when hydrophobic cores from different domains continue through the interface region.

RigidFinder^[77] is a novel method for identification of protein rigid blocks (domains and loops) from two different conformations. Rigid blocks are defined as blocks where all inter residue distances are conserved across conformations.

A general method to identify *dynamical domains*, that is protein regions that behave approximately as rigid units in the course of structural fluctuations, has been introduced by Potestio et al.^[55] and, among other applications was also used to compare the consistency of the dynamics-based domain subdivisions with standard structure-based ones. The method, termed PiSQRD^[78], is publicly available in the form of a webserver^[76]. The latter allows users to optimally subdivide single-chain or multimeric proteins into quasi-rigid domains^[55] ^[76] based on the collective modes of fluctuation of the system. By default the latter are calculated through an elastic network model^[77]; alternatively pre-calculated essential dynamical spaces can be uploaded by the user.

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External links

- The Protein Families (Pfam) database clan browser (<http://www.sanger.ac.uk/Software/Pfam/browse/clans.shtml#159>) provides easy access to information about protein structural domains. A clan contains two or more **Pfam** families that have arisen from a single evolutionary origin.

Structural domain databases

- Conserved Domains at the National Center for Biotechnology website (<http://www.ncbi.nlm.nih.gov/books/bv.fcgi?call=bv.View..ShowSection&rid=handbook.section.110>)
- 3Dee (<http://www.compbio.dundee.ac.uk/3Dee/>)
- CATH (<http://www.cathdb.info/>)
- DALI (http://ekhidna.biocenter.helsinki.fi/dali_server/)
- SCOP (<http://scop.mrc-lmb.cam.ac.uk/scop>)
- Pawson Lab - Protein interaction domains (http://pawsonlab.mshri.on.ca/index.php?option=com_content&task=view&id=30&Itemid=63/)
- Nash Lab - Protein interaction domains in Signal Transduction (http://nashlab.bsd.uchicago.edu/index.php?option=com_content&task=section&id=4&Itemid=29)
- Definition and assignment of structural domains in proteins (<http://realm.sdsc.edu/pdomains/>).

Sequence domain databases

- InterPro (<http://www.ebi.ac.uk/interpro>)
- Pfam (<http://pfam.sanger.ac.uk/>)
- PROSITE (<http://www.expasy.org/prosite/>)
- ProDom (<http://prodom.prabi.fr>)
- SMART (<http://SMART.embl-heidelberg.de>)
- NCBI Conserved Domain Database (<http://www.ncbi.nlm.nih.gov:80/Structure/cdd/cdd.shtml>)
- SUPERFAMILY (<http://supfam.org/SUPERFAMILY>) Library of HMMs representing superfamilies and database of (superfamily and family) annotations for all completely sequenced organisms

Molecular Structure of Nucleic Acids: A Structure for Deoxyribose Nucleic Acid

The *Molecular structure of Nucleic Acids: A Structure for Deoxyribose Nucleic Acid* was an article published by James D. Watson and Francis Crick in the scientific journal *Nature* in its 171st volume on page 737-738 (dated April 25, 1953).^[1] It was the first publication which described the discovery of the double helix structure of DNA. This discovery had a major impact on biology, particularly in the field of genetics.

This article is often termed a "pearl" of science because it is brief and contains the answer to a fundamental mystery about living organisms. This mystery was the question of how it was possible that genetic instructions were held inside organisms and how they were passed from generation to generation. The article presents a simple and elegant solution, which surprised many biologists at the time who felt that DNA transmission was going to be more difficult to detail and understand.

The nature of the discovery

Watson and Crick's 1953 article contains the answer to a fundamental mystery about living organisms. The nature of their discovery was distinctive and in some ways unsurprising. What is hidden in the technical jargon of the title is that Watson and Crick's discovery of the chemical structure of DNA finally revealed how genetic instructions are stored inside organisms and passed from generation to generation. However, Watson and Crick took the majority of their information from a little known scientist named Rosalind Franklin, without her knowledge. She discovered the exact structure of DNA before either of the two, however she died before the public could find out about her. Watson never and to this day, has not given her credit for the discovery.

Origins of molecular biology

The application of physics and chemistry to biological problems led to the development of molecular biology. Not all biology that concerns molecules falls into the category that is labelled "molecular biology".

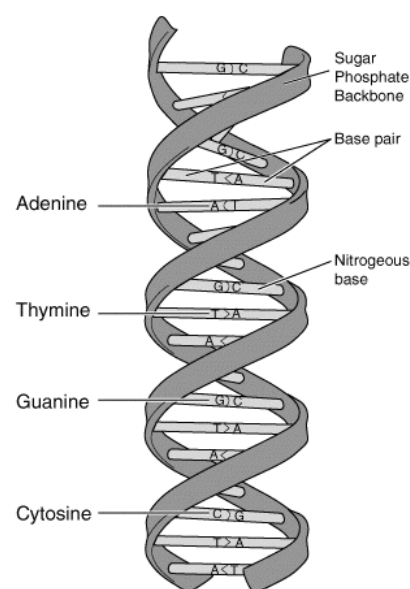


Figure 2. Diagrammatic representation of the key structural features of the DNA double helix. This figure does not depict B-DNA.

Molecular biology is particularly concerned with the flow and consequences of biological information at the level of genes and proteins. The discovery of the DNA double helix made clear that genes are functionally defined parts of DNA molecules and that there must be a way for cells to make use of their DNA genes in order to make proteins.

Linus Pauling was a chemist who was very influential in developing an understanding of the structure of biological molecules. In 1951, Pauling published the structure of the alpha helix, a fundamentally important structural component of proteins. Early in 1953 Pauling published an incorrect triple helix model of DNA.^[2] Both Crick, and particularly Watson, felt that they were racing against Pauling to discover the structure of DNA.

Max Delbrück was a physicist who recognized some of the biological implications of quantum physics. Delbrück's thinking about the physical basis of life stimulated Erwin Schrödinger to write the highly influential book, *What Is Life?* Schrödinger's book was an important influence on Francis Crick, James D. Watson, and Maurice Wilkins who won a Nobel prize in Medicine for the discovery of the DNA double helix. Delbrück's efforts to promote the "Phage Group" (exploring genetics by way of the viruses that infect bacteria) was important in the early development of molecular biology in general and the development of Watson's scientific interests in particular.^[3]

DNA structure and function

It is not always the case that the structure of a molecule is easy to relate to its function. What makes the structure of DNA so obviously related to its function was described modestly at the end of the article: "It has not escaped our notice that the specific pairing we have postulated immediately suggests a possible copying mechanism for the genetic material".

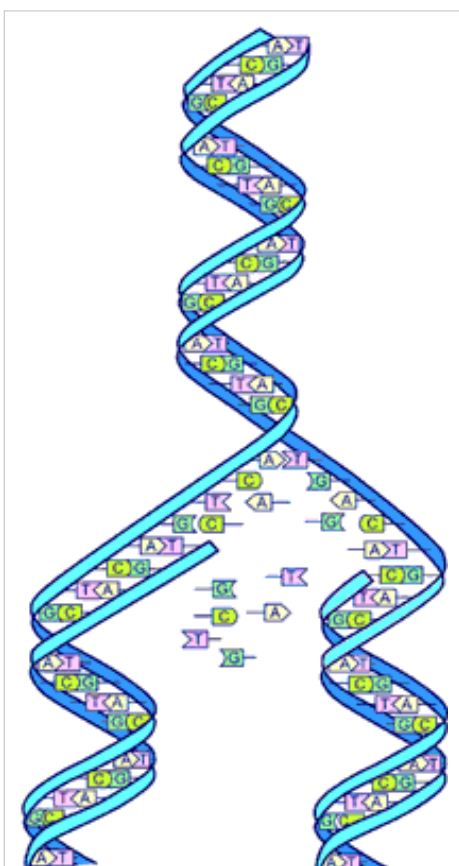


Figure 3. DNA replication. The two base-pair complementary chains of the DNA molecule allow for replication of the genetic instructions.

The "specific pairing" is a key feature of the Watson and Crick model of DNA, the pairing of nucleotide subunits.^[4] In DNA, the amount of guanine is equal to cytosine and the amount of adenine is equal to thymine. The A:T and C:G pairs are structurally similar. In particular, the length of each base pair is the same and they fit equally between the two phosphate backbones (Figure 2). The base pairs are held together by hydrogen bonds, a type of chemical attraction that is easy to break and easy to reform. After realizing the structural similarity of the A:T and C:G pairs, Watson and Crick soon produced their double helix model of DNA with the hydrogen bonds at the core of the helix providing a way to unzip the two complementary strands for easy replication: the last key requirement for a likely model of the genetic molecule.

Indeed, the base-pairing did suggest a way to copy a DNA molecule. Just pull apart the two phosphate backbones, each with its hydrogen bonded A, T, G, and C components. Each strand could then be used as a template for assembly of a new base-pair complementary strand.

Future considerations

When Watson and Crick produced their double helix model of DNA, it was known that most of the specialized features of the many different life forms on Earth are made possible by proteins. Structurally, proteins are long chains of amino acid subunits. In some way, the genetic molecule, DNA, had to contain instructions for how to make

the thousands of proteins found in cells. From the DNA double helix model, it was clear that there must be some correspondence between the linear sequences of nucleotides in DNA molecules to the linear sequences of amino acids in proteins. The details of how sequences of DNA instruct cells to make specific proteins was worked out by molecular biologists during the period from 1953 to 1965. Francis Crick played an integral role in both the theory and analysis of the experiments that led to an improved understanding of the genetic code^[5].

Consequences

Other advances in molecular biology stemming from the discovery of the DNA double helix eventually led to ways to sequence genes. James Watson played an important role in getting government funding for the Human Genome Project. The ability to sequence and manipulate DNA is now central to the biotechnology industry and modern medicine. The austere beauty of the structure and the practical implications of the DNA double helix combined to make *Molecular structure of Nucleic Acids; A Structure for Deoxyribose Nucleic Acid* one of the most prominent biology articles of the twentieth century.

Controversy

Watson and Crick based their molecular model of the DNA double helix on data that had been collected by researchers in several other laboratories. Watson and Crick were the first to put together all of the scattered fragments of information that were required to produce a successful molecular model of DNA.

Much of the data that were used by Crick and Watson came from unpublished work by Maurice Wilkins, Rosalind Franklin, A.R. Stokes, and H.R. Wilson at King's College London in the University of London. Key data from Wilkins, Stokes, and Wilson, and, separately, by Franklin and Gosling, were published in two separate additional articles in the same issue of *Nature* with the article by Watson and Crick.^{[6] [7]} The article by Watson and Crick did acknowledge that they had been "stimulated" by experimental results from the King's College researchers, and a similar acknowledgment was published by M. H. F. Wilkins, A.R. Stokes, and H. R. Wilson in the following three-page article.

In 1968, Watson published a highly controversial^{[8] [9]} autobiographical account of the discovery of the double-helical, molecular structure of DNA called *The Double Helix*, and which was not accepted—at least publicly—either by Francis Crick or by M.H.F. Wilkins. Furthermore, Erwin Chargaff also printed a rather "unsympathetic review" of James D. Watson's booklet in the March 29, 1968 issue of *Science*. In his 'autobiographical' booklet, Watson stated among other things that he and Crick had access to some of Franklin's data from a source that she was not aware of, and also that he had seen—without her permission—the B-DNA X-ray diffraction pattern obtained by Franklin and Gosling in May 1952 at King's in London. In particular, in late 1952, Dr. Franklin had submitted a progress report to the Medical Research Council, which was reviewed by Dr. Max Perutz, then at The Cavendish Laboratory of the University of Cambridge, UK. Watson and Crick also worked in the MRC-supported Cavendish Laboratory in Cambridge whereas Drs. Wilkins and Franklin were in the MRC supported laboratory at King's in London. Such MRC reports were not usually widely circulated, but Crick read a copy of Dr. Franklin's research summary in early 1953^{[10] [11]}.

Max Perutz's justification for passing this information to both Crick and Watson was that the report contained information which Watson has previously heard in November 1951 when Dr. Franklin talked about her unpublished results with Raymond Gosling during a meeting arranged by Dr. M.H.F. Wilkins at King's College, following a request from Crick and Watson; this justification does not hold however for Crick who was not present at this November 1951 meeting, but who also was given access by Max Perutz to Franklin's MRC report data which prompted Crick and Watson to seek permission from Sir Lawrence Bragg—who was at the time the head of the Cavendish Laboratory in Cambridge—to publish in *Nature* their double-helix molecular model of DNA based on Franklin's and also Wilkins's data. Moreover, in November 1951 Watson had acquired—by his own admission—little training in X-ray crystallography, and therefore had not fully understood (again, according to his

own admission, in "The Double Helix") what Dr. Franklin was saying about the structural symmetry of the DNA molecule. Crick, however, knowing the Fourier transforms of Bessel functions that represent the X-ray diffraction patterns of helical structures of atoms, correctly interpreted further one of Dr. Franklin's experimental findings as indicating that DNA was most likely to be a double helix with the two polynucleotide chains running in opposite directions. Crick was thus in a unique position to make this interpretation because he had previously worked on the X-ray diffraction data for other large molecules that had similar, helical symmetry to that of DNA. Dr. Franklin, on the other hand, rejected at first the molecular model building approach proposed by Crick and Watson because their first DNA model presented by Watson to her and Dr. M.H.F. Wilkins in 1952 in London had an obviously incorrect structure with hydrated charged groups on the inside of the model, rather than on the outside, as explicitly admitted by James D. Watson in his "Double Helix" booklet.^[12] It is therefore questioned whether Crick's colleague, Dr. Max Perutz, acted unethically^[13] by allowing Crick access to Dr. Franklin's MRC report about the crystallographic unit of the B-DNA and A-DNA structures. Dr. Perutz claimed, however, that he felt he had not because this report was not confidential, and had been designed as part of an effort to promote contact between different MRC research groups.^[14]

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External links

- Annotated copy of the article (<http://www.exploratorium.edu/origins/coldspring/ideas/printit.html>) from San Francisco's Exploratorium
- Access Excellence Classic Collection article on DNA structure (http://www.accessexcellence.org/AE/AEC/CC/DNA_structure.html).
- Linus Pauling and the Race for DNA: A Documentary History (<http://osulibrary.oregonstate.edu/specialcollections/coll/pauling/dna/index.html>)

Online versions of the article

- Online version (Original text) at nature.com (<http://www.nature.com/nature/dna50/watsoncrick.pdf>)
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Nucleic acid structure prediction

Nucleic acid structure prediction is a computational method to determine nucleic acid secondary and tertiary structure from its sequence. Secondary structure can be predicted from a single or from several nucleic acid sequences. Tertiary structure can be predicted from the sequence, or by comparative modeling (when the structure of a homologous sequence is known).

The problem of predicting nucleic acid secondary structure is dependent mainly on base pairing and base stacking interactions; many molecules have several possible three-dimensional structures, so predicting these structures remains out of reach unless obvious sequence and functional similarity to a known class of nucleic acid molecules, such as transfer RNA or microRNA, is observed. Many secondary structure prediction methods rely on variations of dynamic programming and therefore are unable to efficiently identify pseudoknots.

While the methods are similar, there are slight differences in the approaches to RNA and DNA structure prediction. *In vivo*, DNA structures are more likely to be duplexes with full complementarity between two strands, while RNA structures are more likely to fold into complex secondary and tertiary structures such as in the ribosome, spliceosome, or tRNA. This is partially because the extra oxygen in RNA increases the propensity for hydrogen bonding in the nucleic acid backbone. The energy parameters are also different for the two nucleic acids.

Single sequence structure prediction

A common problem for researchers working with RNA is to determine the three-dimensional structure of the molecule given just the nucleic acid sequence. However, in the case of RNA much of the final structure is determined by the secondary structure or intra-molecular base-pairing interactions of the molecule. This is shown by the high conservation of base-pairings across diverse species.

The most stable structure

Secondary structure of small RNA molecules is largely determined by strong, local interactions such as hydrogen bonds and base stacking. Summing the free energy for such interactions should provide an approximation for the stability of a given structure. To predict the folding free energy of a given secondary structure, an empirical nearest-neighbor model is used. In the nearest neighbor model the free energy change for each motif depends on the sequence of the motif and of its closest base-pairs.^[1] The model and parameters of minimal energy for

Watson–Crick pairs, GU pairs and loop regions were derived from empirical calorimetric experiments, the most up-to-date parameters were published in 2004,^[2] although most software packages use the previous set assembled in 1999.^[3]

The simplest way to find the lowest free energy structure would be to generate all possible structures and calculate the free energy for it, but the number of possible structures for a sequence increases exponentially with the length of RNA (Number of secondary structures = $(1,8)^N$, N- number of nucleotides).^[4] For longer RNA molecules, the number of possible secondary structures is huge: a sequence of 100 nucleotides has more than 1025 possible secondary structures.^[1]

Dynamic programming algorithms

The first and the most popular method for finding the most stable structure is a dynamic programming algorithm.^[5] ^[6] One of the first attempts to predict RNA secondary structure was made by Ruth Nussinov and co-workers who used the dynamic programming method for maximizing the number of base-pairs.^[5] However, there are several issues with this approach: most importantly, the solution is not unique. Nussinov et al. published an adaptation of their approach using a simple nearest-neighbour energy model in 1980.^[6] In 1981, Michael Zuker and Patrick Stiegler proposed using a slightly refined dynamic programming approach to modelling nearest neighbor energy interactions that directly incorporates stacking into the prediction.^[7]

Dynamic programming algorithms provide a means to implicitly check all variants of possible RNA secondary structures without explicitly generating the structures. First, the lowest conformational free energy is determined for each possible sequence fragment starting with the shortest fragments and then for longer fragments. For longer fragments, recursion on the optimal free energy changes determined for shorter sequences speeds the determination of the lowest folding free energy. Once the lowest free energy of the complete sequence is calculated, the exact structure of RNA molecule is determined.^[1]

Dynamic programming algorithms are commonly used to detect base pairing patterns that are "well-nested", that is, form hydrogen bonds only to bases that do not overlap one another in sequence position. Secondary structures that fall into this category include double helices, stem-loops, and variants of the "cloverleaf" pattern found in transfer RNA molecules. These methods rely on pre-calculated parameters which estimate the free energy associated with particular types of base-pairing interactions, including Watson-Crick and Hoogsteen base pairs. Depending on the complexity of the method, single base pairs may be considered as well as short two- or three-base segments to incorporate the effects of base stacking. This method cannot identify pseudoknots, which are not well nested, without substantial algorithmic modifications that are extremely computationally expensive.^[8]

Suboptimal structures

The accuracy of RNA secondary structure prediction from a single sequence by free energy minimization is limited by several factors:

1. The free energy value's list in nearest neighbor model is incomplete
2. Not all known RNA folds in such a way as to conform with the thermodynamic minimum.
3. Some RNA sequences have more than one biologically active conformation (e. i. Riboswitches)

For this reason, the ability to predict structures which have similar low free energy would provide significant information. Such structures are termed suboptimal structures. MFOLD is one program that generates suboptimal structures.^[9]

Predicting pseudoknots

One of the issues when predicting RNA secondary structure is that the standard free energy minimization and statistical sampling methods can not find pseudoknots.^[3] The major problem is that the usual dynamic programming algorithms, when predicting secondary structure, consider only the interactions between the closest nucleotides, while pseudoknotted structures are formed due to interactions between distant nucleotides. Rivas and Eddy published a dynamic programming algorithm for predicting pseudoknots.^[8] However, this dynamic programming algorithm is very slow. The standard dynamic programming algorithm for free energy minimization scales $O(N^3)$ in time (N is the number of nucleotides in the sequence), while the Rivas and Eddy algorithm scales $O(N^6)$ in time. This has prompted several researchers to implement versions of the algorithm that restrict classes of pseudoknots, resulting in performance gains. For example, pknotsRG tool includes only the class of simple recursive pseudoknots and scales $O(N^4)$ in time.^[10]

Other approaches for RNA secondary structure prediction

Another approach for RNA secondary structure determination is to sample structures from the Boltzmann ensemble,^{[11] [12]} as exemplified by the program SFOLD. The program generates a statistical sample of all possible RNA secondary structures. The algorithm samples secondary structures according to the Boltzmann distribution. The sampling method offers an appealing solution to the problem of uncertainties in folding.^[12]

Comparative secondary structure prediction

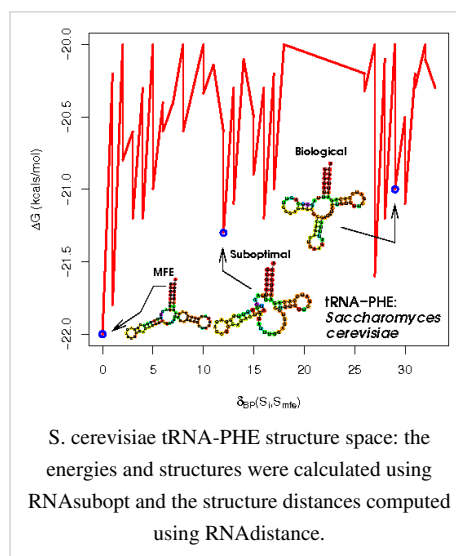
Sequence covariation methods rely on the existence of a data set composed of multiple homologous RNA sequences with related but dissimilar sequences. These methods analyze the covariation of individual base sites in evolution; maintenance at two widely separated sites of a pair of base-pairing nucleotides indicates the presence of a structurally required hydrogen bond between those positions. The general problem of pseudoknot prediction has been shown to be NP-complete.^[13]

In general, the problem of alignment and consensus structure prediction are closely related. Three different approaches to the prediction of consensus structures can be distinguished:^[14]

1. Folding of alignment
2. Simultaneous sequence alignment and folding
3. Alignment of predicted structures

Align then fold

A practical heuristic approach is to use multiple sequence alignment tools to produce an alignment of several RNA sequences, to find consensus sequence and then fold it. The quality of the alignment determines the accuracy of the consensus structure model. Consensus sequences are folded using various approaches similarly as in individual structure prediction problem. The thermodynamic folding approach is exemplified by RNAalifold program.^[15] The different approaches are exemplified by Pfold and ILM programs. Pfold program implements a SCFGs.^[16] ILM (iterated loop matching) unlike the other algorithms for folding of alignments, can return pseudocnotted structures. It uses combination of thermodynamics and mutual information content scores.^[17]



Align and fold

Evolution frequently preserves functional RNA structure better than RNA sequence.^[15] Hence, a common biological problem is to infer a common structure for two or more highly diverged but homologous RNA sequences. In practice, sequence alignments become unsuitable and do not help to improve the accuracy of structure prediction, when sequence similarity of two sequences is less than 50%.^[18]

Structure-based alignment programs improves the performance of these alignments and most of them are variants of the Sankoff algorithm^[19]. Basically, Sankoff algorithm is a merger of sequence alignment and Nussinov^[5] (maximal-pairing) folding dynamic programming method.^[20] Sankoff algorithm itself is a theoretical exercise because it requires extreme computational resources ($O(n^3m)$ in time, and $O(n^2m)$ in space, where n is the sequence length and m is the number of sequences). Some notable attempts at implementing restricted versions of Sankoff's algorithm are Foldalign,^{[21] [22]} Dynalign,^{[23] [24]} PMmulti/PMcomp,^[20] Stemloc,^[25] and Murlet.^[26] In these implementations the maximal length of alignment or variants of possible consensus structures are restricted. For example, Foldalign focuses on local alignments and restricts the possible length of the sequences alignment.

Fold then align

A less widely used approach is to fold the sequences using single sequence structure prediction methods and align the resulting structures using tree-based metrics.^[27] The fundamental weakness with this approach is that single sequence predictions are often inaccurate, thus all further analyses are affected.

Tertiary structure prediction

Once secondary structure of RNA is known, the next challenge is to predict tertiary structure. The biggest problem is to determine the structure of regions between double stranded helical regions. Also RNA molecules often contain posttranscriptionally modified nucleosides, which because of new possible non-canonical interactions, cause a lot of troubles for tertiary structure prediction.^{[28] [29] [30] [31]}

See also

- RNA
- RNA structure
- Non-coding RNA
- List of RNA structure prediction software
- List of nucleic acid simulation software

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Nucleic Acids

Nucleic acids are biological molecules essential for life, and include DNA (deoxyribonucleic acid) and RNA (ribonucleic acid). Together with proteins, nucleic acids make up the most important macromolecules; each is found in abundance in all living things. Nucleic acids were first discovered by Friedrich Miescher in 1871.^[1] Experimental studies of nucleic acids constitute a major part of modern biological and medical research, and form a foundation for genome and forensic science, as well as the biotechnology and pharmaceutical industries.^{[2] [3] [4]}

Occurrence and nomenclature ^[5]

The term *nucleic acid* is the over all name for DNA and RNA, members of a family of biopolymers^[6], and is synonymous with *polynucleotide*. Nucleic acids were named for their initial discovery within the cell nucleus, and for the presence of phosphate groups (related to phosphoric acid). Although first discovered within the nucleus of eukaryotic cells, nucleic acids are now known to be found in all life forms, including within bacteria, archaea, mitochondria, chloroplasts, viruses and viroids. All living cells and organelles contain both DNA and RNA, while viruses contain either DNA or RNA, but not usually both^[7]. The basic component of biological nucleic acids is the nucleotide, each of which contains a pentose sugar (ribose or deoxyribose), a phosphate group, and a nucleobase. Nucleic acids are also generated within the laboratory, through the use of enzymes^[8] (DNA and RNA polymerases) and by solid-phase chemical synthesis. The chemical methods also enable the generation of altered nucleic acids that are not found in nature^[9], for example peptide nucleic acids.

Molecular composition and size ^[10]

Nucleic acids can vary in size, but are generally very large molecules. Indeed, DNA molecules are probably the largest individual molecules known. Well-studied biological nucleic acid molecules range in size from 21 nucleotides (small interfering RNA) to large chromosomes (human chromosome 1 is a single molecule that contains 247 million base pairs^[11]).

In most cases, naturally occurring DNA molecules are double-stranded and RNA molecules are single-stranded. There are numerous exceptions, however--some viruses have genomes made of double-stranded RNA and other viruses have single-stranded DNA genomes, and, in some circumstances, nucleic acid structures with three or four strands can form.

Nucleic acids are linear polymers (chains) of nucleotides. Each nucleotide consists of three components: a purine or pyrimidine nucleobase (sometimes termed *nitrogenous base* or simply *base*), a pentose sugar; and a phosphate group. The substructure consisting of a nucleobase plus sugar is termed a nucleoside. Nucleic acid types differ in the structure of the sugar in their nucleotides - DNA contains 2'-deoxyribose while RNA contains ribose (where the only difference is the presence of a hydroxyl group). Also, the nucleobases found in the two nucleic acid types are different: adenine, cytosine, and guanine are found in both RNA and DNA, while thymine occurs in DNA and uracil occurs in RNA.

The sugars and phosphates in nucleic acids are connected to each other in an alternating chain (sugar-phosphate backbone) through phosphodiester linkages^[10]. In conventional nomenclature, the carbons to which the phosphate groups attach are the 3'-end and the 5'-end carbons of the sugar. This gives nucleic acids directionality, and the ends of nucleic acid molecules are referred to as 5'-end and 3'-end. The nucleobases are joined to the sugars via an N-glycosidic linkage involving a nucleobase ring nitrogen (N-1 for pyrimidines and N-9 for purines) and the 1' carbon of the pentose sugar ring.

Non-standard nucleosides are also found in both RNA and DNA and usually arise from modification of the standard nucleosides within the DNA molecule or the primary (initial) RNA transcript. Transfer RNA (tRNA) molecules contain a particularly large number of modified nucleosides.^[12]

Topology

Double-stranded nucleic acids are made up of complementary sequences, in which extensive Watson-Crick base pairing results in the formation of a highly repeated and quite uniform double-helical three-dimensional structure.^[13] In contrast, single-stranded RNA and DNA molecules are not constrained to a regular double helix, and can adopt highly complex three-dimensional structures that are based on short stretches of intramolecular base-paired sequences that include both Watson-Crick and noncanonical base pairs, as well as a wide range of complex tertiary interactions.^[14]

Nucleic acid molecules are usually unbranched, and may occur as linear and circular molecules. For example, bacterial chromosomes, plasmids, mitochondrial DNA and chloroplast DNA are usually circular double-stranded DNA molecules, while chromosomes of the eukaryotic nucleus are usually linear double-stranded DNA molecules^[15]. Most RNA molecules are linear, single-stranded molecules, but both circular and branched molecules can result from RNA splicing reactions.^[5]

Nucleic acid sequences

One DNA or RNA molecule differs from another primarily in the sequence of nucleotides. Nucleotide sequences are of great importance in biology, since they carry the ultimate instructions that encode all biological molecules, molecular assemblies, subcellular and cellular structures, organs and organisms, and directly enable cognition, memory and behavior (See: Genetics). Enormous efforts have gone into the development of experimental methods to determine the nucleotide sequence of biological DNA and RNA molecules^{[16] [17]}, and today hundreds of millions

of nucleotides are sequenced daily at genome centers and smaller laboratories worldwide.

Types of nucleic acids

Deoxyribonucleic acid

Deoxyribonucleic acid is a nucleic acid that contains the genetic instructions used in the development and functioning of all known living organisms. The main role of DNA molecules is the long-term storage of information and DNA is often compared to a set of blueprints, since it contains the instructions needed to construct other components of cells, such as proteins and RNA molecules. The DNA segments that carry this genetic information are called genes, but other DNA sequences have structural purposes, or are involved in regulating the use of this genetic information.

Ribonucleic acid

Ribonucleic acid (RNA) functions in converting genetic information from genes into the amino acid sequences of proteins. The three universal types of RNA include transfer RNA (tRNA), messenger RNA (mRNA), and ribosomal RNA (rRNA). Messenger RNA acts to carry genetic sequence information between DNA and ribosomes, directing protein synthesis. Ribosomal RNA is a major component of the ribosome, and catalyzes peptide bond formation. Transfer RNA serves as the carrier molecule for amino acids to be used in protein synthesis, and is responsible for decoding the mRNA. In addition, many other classes of RNA are now known.

Artificial nucleic acid analogs

Artificial nucleic acid analogs have been designed and synthesized by chemists, and include peptide nucleic acid, morpholino- and locked nucleic acid, as well as glycol nucleic acid and threose nucleic acid. Each of these is distinguished from naturally-occurring DNA or RNA by changes to the backbone of the molecule.

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External links

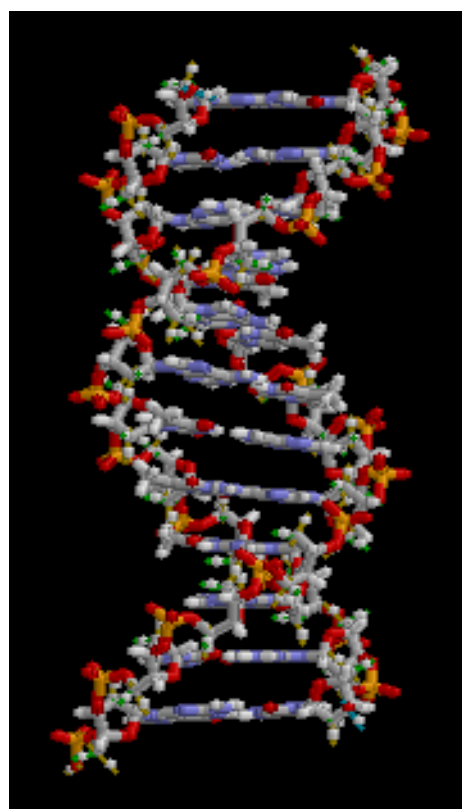
- Interview with Aaron Klug, Nobel Laureate for structural elucidation of biologically important nucleic-acid protein complexes (<http://www.vega.org.uk/video/programme/122>) provided by the Vega Science Trust.
- Nucleic Acids Research (Journal) (<http://nar.oxfordjournals.org/>)

DNA

Deoxyribonucleic acid (English

pronunciation: /diˌɒksiˈraɪbɵnjuːˈkleɪɪk ˈæsɪd/ ( listen)), or **DNA**, is a nucleic acid that contains the genetic instructions used in the development and functioning of all known living organisms, with the exception of some viruses. The main role of DNA molecules is the long-term storage of information. DNA is often compared to a set of blueprints, like a recipe or a code, since it contains the instructions needed to construct other components of cells, such as proteins and RNA molecules. The DNA segments that carry this genetic information are called genes, but other DNA sequences have structural purposes, or are involved in regulating the use of this genetic information.

DNA consists of two long polymers of simple units called nucleotides, with backbones made of sugars and phosphate groups joined by ester bonds. These two strands run in opposite directions to each other and are therefore anti-parallel. Attached to each sugar is one of four types of molecules called bases. It is the sequence of these four bases along the backbone that encodes information. This information is read using the genetic code, which specifies the sequence of the amino acids within proteins. The code is read by copying stretches of DNA into the related nucleic acid RNA, in a process called transcription.



The structure of part of a DNA double helix

Within cells, DNA is organized into long structures called chromosomes. These chromosomes are duplicated before cells divide, in a process called DNA replication. Eukaryotic organisms (animals, plants, fungi, and protists) store

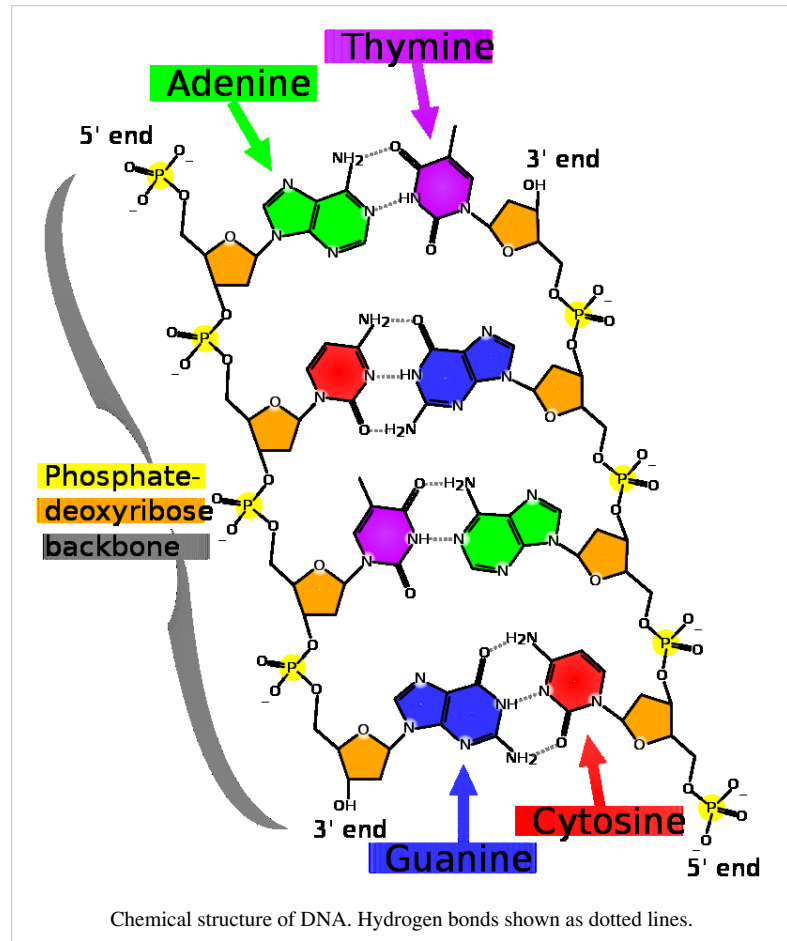
most of their DNA inside the cell nucleus and some of their DNA in organelles, such as mitochondria or chloroplasts.^[1] In contrast, prokaryotes (bacteria and archaea) store their DNA only in the cytoplasm. Within the chromosomes, chromatin proteins such as histones compact and organize DNA. These compact structures guide the interactions between DNA and other proteins, helping control which parts of the DNA are transcribed.

Properties

DNA is a long polymer made from repeating units called nucleotides.^[2] ^[3] ^[4] As first discovered by James D. Watson and Francis Crick, the structure of DNA of all species comprises two helical chains each coiled round the same axis, and each with a pitch of 34 Ångströms (3.4 nanometres) and a radius of 10 Ångströms (1.0 nanometres).^[5] According to another study, when measured in a particular solution, the DNA chain measured 22 to 26 Ångströms wide (2.2 to 2.6 nanometres), and one nucleotide unit measured 3.3 Å (0.33 nm) long.^[6] Although each individual repeating unit is very small, DNA polymers can be very large molecules containing millions of nucleotides. For instance, the largest human chromosome, chromosome number 1, is approximately 220 million base pairs long.^[7]

In living organisms, DNA does not usually exist as a single molecule, but instead as a pair of molecules that are held tightly together.^[5] ^[8] These two long strands entwine like vines, in the shape of a double helix. The nucleotide repeats contain both the segment of the backbone of the molecule, which holds the chain together, and a base, which interacts with the other DNA strand in the helix. A base linked to a sugar is called a nucleoside and a base linked to a sugar and one or more phosphate groups is called a nucleotide. If multiple nucleotides are linked together, as in DNA, this polymer is called a polynucleotide.^[9]

The backbone of the DNA strand is made from alternating phosphate and sugar residues.^[10] The sugar in DNA is 2-deoxyribose, which is a pentose (five-carbon) sugar. The sugars are joined together by phosphate groups that form phosphodiester bonds between the third and fifth carbon atoms of adjacent sugar rings. These asymmetric bonds mean a strand of DNA has a direction. In a double helix the direction of the nucleotides in one strand is opposite to their direction in the other strand: the strands are *antiparallel*. The asymmetric ends of DNA strands are called the 5' (*five prime*) and 3' (*three prime*) ends, with the 5' end having a terminal phosphate group and the 3' end a terminal hydroxyl group. One major difference between DNA and RNA is the sugar, with the 2-deoxyribose in DNA being replaced by the alternative pentose sugar ribose in RNA.^[8]



The DNA double helix is stabilized by hydrogen bonds between the bases attached to the two strands. The four bases found in DNA are adenine (abbreviated A), cytosine (C), guanine (G) and thymine (T). These four bases are attached to the sugar/phosphate to form the complete nucleotide, as shown for adenosine monophosphate.

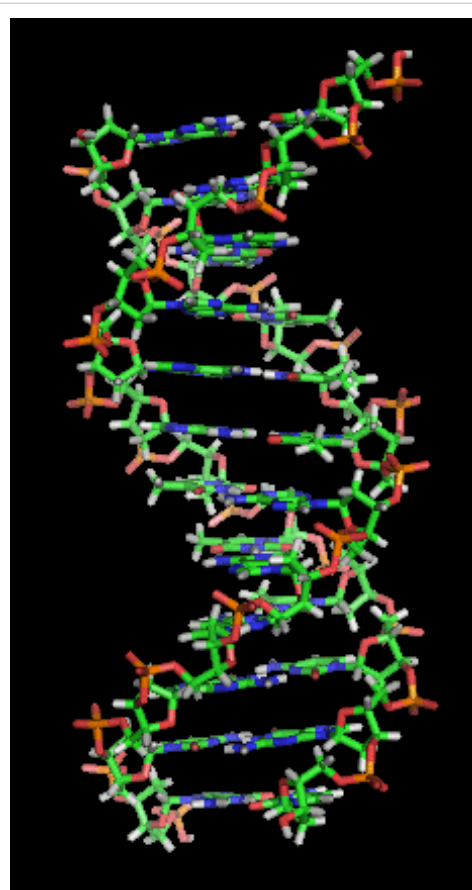
These bases are classified into two types; adenine and guanine are fused five- and six-membered heterocyclic compounds called purines, while cytosine and thymine are six-membered rings called pyrimidines.^[8] A fifth pyrimidine base, called uracil (U), usually takes the place of thymine in RNA and differs from thymine by lacking a methyl group on its ring. Uracil is not usually found in DNA, occurring only as a breakdown product of cytosine. In addition to RNA and DNA, a large number of artificial nucleic acid analogues have also been created to study the properties of nucleic acids, or for use in biotechnology.^[12]

Grooves

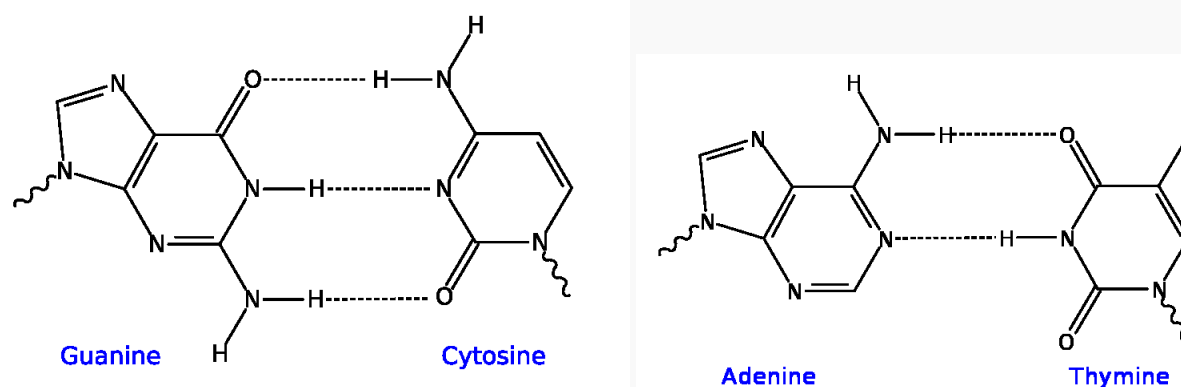
Twin helical strands form the DNA backbone. Another double helix may be found by tracing the spaces, or grooves, between the strands. These voids are adjacent to the base pairs and may provide a binding site. As the strands are not directly opposite each other, the grooves are unequally sized. One groove, the major groove, is 22 Å wide and the other, the minor groove, is 12 Å wide.^[13] The narrowness of the minor groove means that the edges of the bases are more accessible in the major groove. As a result, proteins like transcription factors that can bind to specific sequences in double-stranded DNA usually make contacts to the sides of the bases exposed in the major groove.^[14] This situation varies in unusual conformations of DNA within the cell (*see below*), but the major and minor grooves are always named to reflect the differences in size that would be seen if the DNA is twisted back into the ordinary B form.

Base pairing

Each type of base on one strand forms a bond with just one type of base on the other strand. This is called complementary base pairing. Here, purines form hydrogen bonds to pyrimidines, with A bonding only to T, and C bonding only to G. This arrangement of two nucleotides binding together across the double helix is called a base pair. As hydrogen bonds are not covalent, they can be broken and rejoined relatively easily. The two strands of DNA in a double helix can therefore be pulled apart like a zipper, either by a mechanical force or high temperature.^[15] As a result of this complementarity, all the information in the double-stranded sequence of a DNA helix is duplicated on each strand, which is vital in DNA replication. Indeed, this reversible and specific interaction between complementary base pairs is critical for all the functions of DNA in living organisms.^[3]



A section of DNA. The bases lie horizontally between the two spiraling strands.^[11] Animated version at File:DNA orbit animated.gif.



Top, a GC base pair with three hydrogen bonds. Bottom, an AT base pair with two hydrogen bonds. Non-covalent hydrogen bonds between the pairs are shown as dashed lines.

The two types of base pairs form different numbers of hydrogen bonds, AT forming two hydrogen bonds, and GC forming three hydrogen bonds (see figures, left). DNA with high GC-content is more stable than DNA with low GC-content, but contrary to popular belief, this is not due to the extra hydrogen bond of a GC base pair but rather the contribution of stacking interactions (hydrogen bonding merely provides specificity of the pairing, not stability).^[16]

As a result, it is both the percentage of GC base pairs and the overall length of a DNA double helix that determine the strength of the association between the two strands of DNA. Long DNA helices with a high GC content have stronger-interacting strands, while short helices with high AT content have weaker-interacting strands.^[17] In biology, parts of the DNA double helix that need to separate easily, such as the TATAAT Pribnow box in some promoters, tend to have a high AT content, making the strands easier to pull apart.^[18]

In the laboratory, the strength of this interaction can be measured by finding the temperature required to break the hydrogen bonds, their melting temperature (also called T_m value). When all the base pairs in a DNA double helix melt, the strands separate and exist in solution as two entirely independent molecules. These single-stranded DNA molecules (*ssDNA*) have no single common shape, but some conformations are more stable than others.^[19]

Sense and antisense

A DNA sequence is called "sense" if its sequence is the same as that of a messenger RNA copy that is translated into protein.^[20] The sequence on the opposite strand is called the "antisense" sequence. Both sense and antisense sequences can exist on different parts of the same strand of DNA (i.e. both strands contain both sense and antisense sequences). In both prokaryotes and eukaryotes, antisense RNA sequences are produced, but the functions of these RNAs are not entirely clear.^[21] One proposal is that antisense RNAs are involved in regulating gene expression through RNA-RNA base pairing.^[22]

A few DNA sequences in prokaryotes and eukaryotes, and more in plasmids and viruses, blur the distinction between sense and antisense strands by having overlapping genes.^[23] In these cases, some DNA sequences do double duty, encoding one protein when read along one strand, and a second protein when read in the opposite direction along the other strand. In bacteria, this overlap may be involved in the regulation of gene transcription,^[24] while in viruses, overlapping genes increase the amount of information that can be encoded within the small viral genome.^[25]

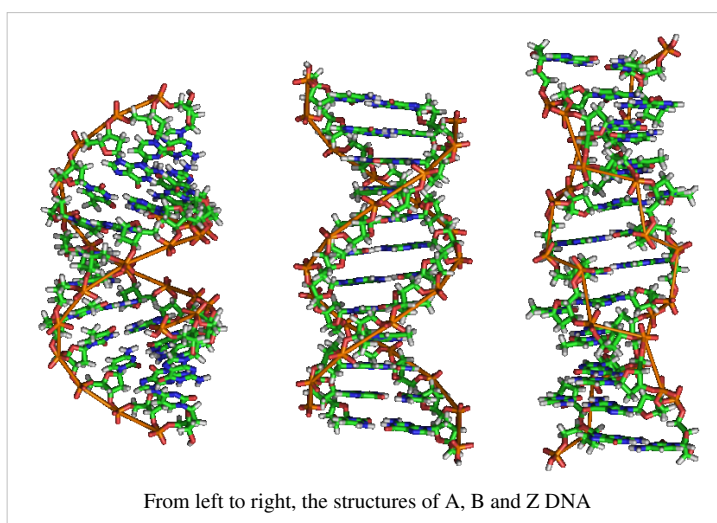
Supercoiling

DNA can be twisted like a rope in a process called DNA supercoiling. With DNA in its "relaxed" state, a strand usually circles the axis of the double helix once every 10.4 base pairs, but if the DNA is twisted the strands become more tightly or more loosely wound.^[26] If the DNA is twisted in the direction of the helix, this is positive supercoiling, and the bases are held more tightly together. If they are twisted in the opposite direction, this is negative supercoiling, and the bases come apart more easily. In nature, most DNA has slight negative supercoiling that is introduced by enzymes called topoisomerases.^[27] These enzymes are also needed to relieve the twisting

stresses introduced into DNA strands during processes such as transcription and DNA replication.^[28]

Alternate DNA structures

DNA exists in many possible conformations that include A-DNA, B-DNA, and Z-DNA forms, although, only B-DNA and Z-DNA have been directly observed in functional organisms.^[10] The conformation that DNA adopts depends on the hydration level, DNA sequence, the amount and direction of supercoiling, chemical modifications of the bases, the type and concentration of metal ions, as well as the presence of polyamines in solution.^[29]

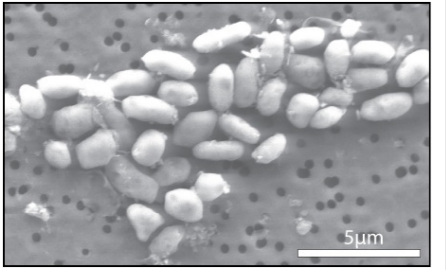


The first published reports of A-DNA X-ray diffraction patterns— and also B-DNA used analyses based on Patterson transforms that provided only a limited amount of structural information for oriented fibers of DNA.^{[30] [31]} An alternate analysis was then proposed by Wilkins *et al.*, in 1953, for the *in vivo* B-DNA X-ray diffraction/scattering patterns of highly hydrated DNA fibers in terms of squares of Bessel functions.^[32] In the same journal, James D. Watson and Francis Crick presented their molecular modeling analysis of the DNA X-ray diffraction patterns to suggest that the structure was a double-helix.^[5]

Although the 'B-DNA form' is most common under the conditions found in cells,^[33] it is not a well-defined conformation but a family of related DNA conformations^[34] that occur at the high hydration levels present in living cells. Their corresponding X-ray diffraction and scattering patterns are characteristic of molecular paracrystals with a significant degree of disorder.^{[35] [36]}

Compared to B-DNA, the A-DNA form is a wider right-handed spiral, with a shallow, wide minor groove and a narrower, deeper major groove. The A form occurs under non-physiological conditions in partially dehydrated samples of DNA, while in the cell it may be produced in hybrid pairings of DNA and RNA strands, as well as in enzyme-DNA complexes.^{[37] [38]} Segments of DNA where the bases have been chemically modified by methylation may undergo a larger change in conformation and adopt the Z form. Here, the strands turn about the helical axis in a left-handed spiral, the opposite of the more common B form.^[39] These unusual structures can be recognized by specific Z-DNA binding proteins and may be involved in the regulation of transcription.^[40]

Alternate DNA chemistry

GFAJ-1	
	
Magnified cells of bacterium GFAJ-1 grown on arsenic. (J. Switzer Blum)	
Scientific classification	
Kingdom:	Bacteria
Phylum:	Proteobacteria
Class:	Gammaproteobacteria
Order:	Oceanospirillales
Family:	Halomonadaceae

For a number of years exobiologists have proposed the existence of a shadow biosphere, a postulated microbial biosphere of Earth that uses radically different biochemical and molecular processes than currently known life. One of the proposals was the existence of lifeforms that use arsenic instead of phosphorus in DNA.

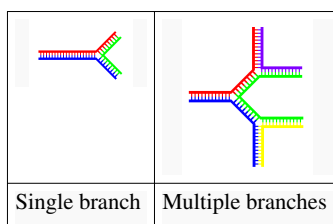
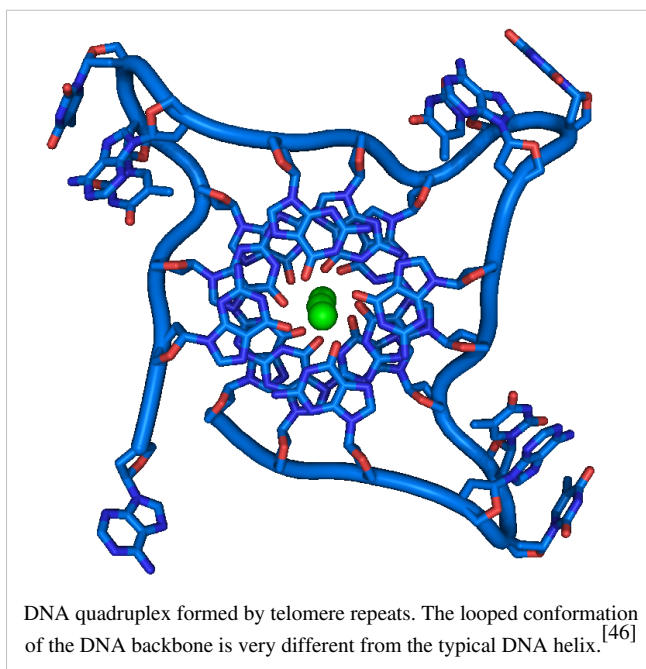
A December 2010 NASA press conference revealed that the bacterium GFAJ-1, which has evolved in an arsenic-rich environment, is the first terrestrial lifeform found which may have this ability. The bacterium was found in Mono Lake, east of Yosemite National Park. GFAJ-1 is a rod-shaped extremophile bacterium in the family Halomonadaceae that, when starved of phosphorus, may be capable of incorporating the usually poisonous element arsenic in its DNA.^[41] This discovery lends weight to the long-standing idea that extraterrestrial life could have a different chemical makeup from life on Earth.^[41] ^[42] The research was carried out by a team led by Felisa Wolfe-Simon, a geomicrobiologist and geobiochemist, a Postdoctoral Fellow of the NASA Astrobiology Institute with Arizona State University.

Quadruplex structures

At the ends of the linear chromosomes are specialized regions of DNA called telomeres. The main function of these regions is to allow the cell to replicate chromosome ends using the enzyme telomerase, as the enzymes that normally replicate DNA cannot copy the extreme 3’ ends of chromosomes.^[43] These specialized chromosome caps also help protect the DNA ends, and stop the DNA repair systems in the cell from treating them as damage to be corrected.^[44] In human cells, telomeres are usually lengths of single-stranded DNA containing several thousand repeats of a simple TTAGGG sequence.^[45]

These guanine-rich sequences may stabilize chromosome ends by forming structures of stacked sets of four-base units, rather than the usual base pairs found in other DNA molecules. Here, four guanine bases form a flat plate and these flat four-base units then stack on top of each other, to form a stable *G-quadruplex* structure.^[47] These structures are stabilized by hydrogen bonding between the edges of the bases and chelation of a metal ion in the centre of each four-base unit.^[48] Other structures can also be formed, with the central set of four bases coming from either a single strand folded around the bases, or several different parallel strands, each contributing one base to the central structure.

In addition to these stacked structures, telomeres also form large loop structures called telomere loops, or T-loops. Here, the single-stranded DNA curls around in a long circle stabilized by telomere-binding proteins.^[49] At the very end of the T-loop, the single-stranded telomere DNA is held onto a region of double-stranded DNA by the telomere strand disrupting the double-helical DNA and base pairing to one of the two strands. This triple-stranded structure is called a displacement loop or D-loop.^[47]

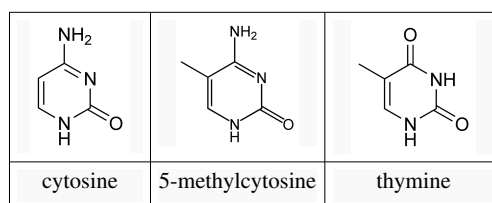


Branched DNA can form networks containing multiple branches.

Branched DNA

In DNA fraying occurs when non-complementary regions exist at the end of an otherwise complementary double-strand of DNA. However, branched DNA can occur if a third strand of DNA is introduced and contains adjoining regions able to hybridize with the frayed regions of the pre-existing double-strand. Although the simplest example of branched DNA involves only three strands of DNA, complexes involving additional strands and multiple branches are also possible.^[50] Branched DNA can be used in nanotechnology to construct geometric shapes, see the section on uses in technology below.

Chemical modifications



Structure of cytosine with and without the 5-methyl group. Deamination converts 5-methylcytosine into thymine.

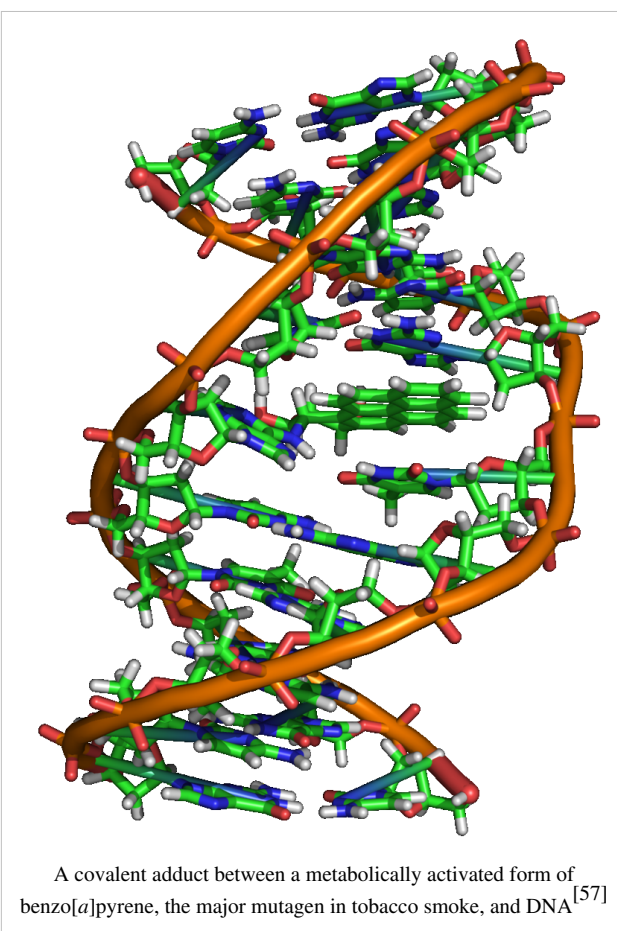
Base modifications

The expression of genes is influenced by how the DNA is packaged in chromosomes, in a structure called chromatin. Base modifications can be involved in packaging, with regions that have low or no gene expression usually containing high levels of methylation of cytosine bases. For example, cytosine methylation, produces 5-methylcytosine, which is important for X-chromosome inactivation.^[51] The average level of methylation varies between organisms - the worm *Caenorhabditis elegans* lacks cytosine methylation, while vertebrates have higher levels, with up to 1% of their DNA containing 5-methylcytosine.^[52] Despite the importance of 5-methylcytosine, it can deaminate to leave a thymine base, so methylated cytosines are particularly prone to mutations.^[53] Other base modifications include adenine methylation in bacteria, the presence of 5-hydroxymethylcytosine in the brain,^[54] and the glycosylation of uracil to produce the "J-base" in kinetoplasts.^{[55] [56]}

Damage

DNA can be damaged by many sorts of mutagens, which change the DNA sequence. Mutagens include oxidizing agents, alkylating agents and also high-energy electromagnetic radiation such as ultraviolet light and X-rays. The type of DNA damage produced depends on the type of mutagen. For example, UV light can damage DNA by producing thymine dimers, which are cross-links between pyrimidine bases.^[58] On the other hand, oxidants such as free radicals or hydrogen peroxide produce multiple forms of damage, including base modifications, particularly of guanosine, and double-strand breaks.^[59] A typical human cell contains about 150,000 bases that have suffered oxidative damage.^[60] Of these oxidative lesions, the most dangerous are double-strand breaks, as these are difficult to repair and can produce point mutations, insertions and deletions from the DNA sequence, as well as chromosomal translocations.^[61]

Many mutagens fit into the space between two adjacent base pairs, this is called *intercalation*. Most intercalators are aromatic and planar molecules; examples include ethidium bromide, daunomycin, and doxorubicin. In order for an intercalator to fit between base pairs, the bases must separate, distorting the DNA strands by unwinding of the double helix. This inhibits both transcription and DNA replication, causing toxicity and mutations. As a result, DNA intercalators are often carcinogens, and benzo[*a*]pyrene diol epoxide, acridines, aflatoxin and ethidium bromide are well-known examples.^{[62] [63] [64]} Nevertheless, due to their ability to inhibit DNA transcription and replication, other similar toxins are also used in chemotherapy to inhibit rapidly growing cancer cells.^[65]



Biological functions

DNA usually occurs as linear chromosomes in eukaryotes, and circular chromosomes in prokaryotes. The set of chromosomes in a cell makes up its genome; the human genome has approximately 3 billion base pairs of DNA

arranged into 46 chromosomes.^[66] The information carried by DNA is held in the sequence of pieces of DNA called genes. Transmission of genetic information in genes is achieved via complementary base pairing. For example, in transcription, when a cell uses the information in a gene, the DNA sequence is copied into a complementary RNA sequence through the attraction between the DNA and the correct RNA nucleotides. Usually, this RNA copy is then used to make a matching protein sequence in a process called translation, which depends on the same interaction between RNA nucleotides. In alternative fashion, a cell may simply copy its genetic information in a process called DNA replication. The details of these functions are covered in other articles; here we focus on the interactions between DNA and other molecules that mediate the function of the genome.

Genes and genomes

Genomic DNA is tightly and orderly packed in the process called DNA condensation to fit the small available volumes of the cell. In eukaryotes, DNA is located in the cell nucleus, as well as small amounts in mitochondria and chloroplasts. In prokaryotes, the DNA is held within an irregularly shaped body in the cytoplasm called the nucleoid.^[67] The genetic information in a genome is held within genes, and the complete set of this information in an organism is called its genotype. A gene is a unit of heredity and is a region of DNA that influences a particular characteristic in an organism. Genes contain an open reading frame that can be transcribed, as well as regulatory sequences such as promoters and enhancers, which control the transcription of the open reading frame.

In many species, only a small fraction of the total sequence of the genome encodes protein. For example, only about 1.5% of the human genome consists of protein-coding exons, with over 50% of human DNA consisting of non-coding repetitive sequences.^[68] The reasons for the presence of so much non-coding DNA in eukaryotic genomes and the extraordinary differences in genome size, or *C-value*, among species represent a long-standing puzzle known as the "C-value enigma".^[69] However, DNA sequences that do not code protein may still encode functional non-coding RNA molecules, which are involved in the regulation of gene expression.^[70]



Some non-coding DNA sequences play structural roles in chromosomes. Telomeres and centromeres typically contain few genes, but are important for the function and stability of chromosomes.^{[44] [72]} An abundant form of non-coding DNA in humans are pseudogenes, which are copies of genes that have been disabled by mutation.^[73] These sequences are usually just molecular fossils, although they can occasionally serve as raw genetic material for the creation of new genes through the process of gene duplication and divergence.^[74]

Transcription and translation

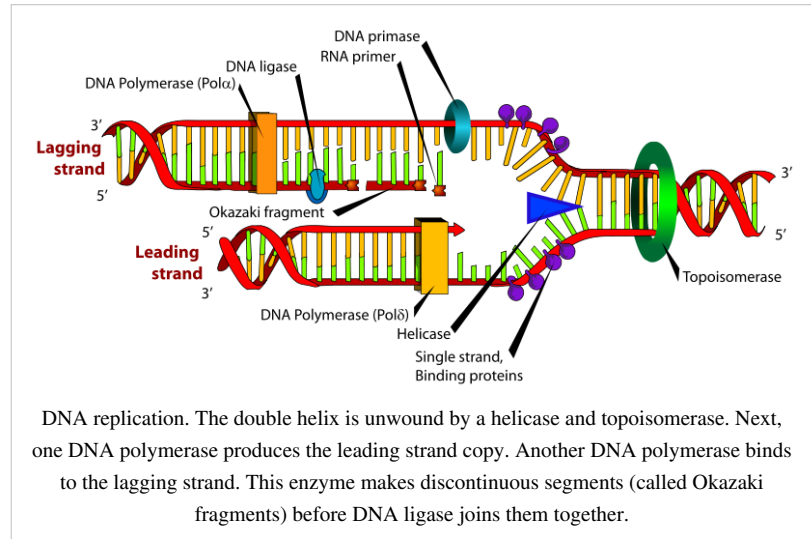
A gene is a sequence of DNA that contains genetic information and can influence the phenotype of an organism. Within a gene, the sequence of bases along a DNA strand defines a messenger RNA sequence, which then defines one or more protein sequences. The relationship between the nucleotide sequences of genes and the amino-acid sequences of proteins is determined by the rules of translation, known collectively as the genetic code. The genetic code consists of three-letter 'words' called *codons* formed from a sequence of three nucleotides (e.g. ACT, CAG, TTT).

In transcription, the codons of a gene are copied into messenger RNA by RNA polymerase. This RNA copy is then decoded by a ribosome that reads the RNA sequence by base-pairing the messenger RNA to transfer RNA, which carries amino acids. Since there are 4 bases in 3-letter combinations, there are 64 possible codons (4^3 combinations). These encode the twenty standard amino acids, giving most amino acids more than one possible codon. There are also three 'stop' or 'nonsense' codons signifying the end of the coding region; these are the TAA, TGA and TAG codons.

Replication

Cell division is essential for an organism to grow, but, when a cell divides, it must replicate the DNA in its genome so that the two daughter cells have the same genetic information as their parent. The double-stranded structure of DNA provides a simple mechanism for DNA replication. Here, the two strands are separated and then each strand's complementary DNA sequence is recreated by an enzyme called DNA polymerase. This enzyme makes the

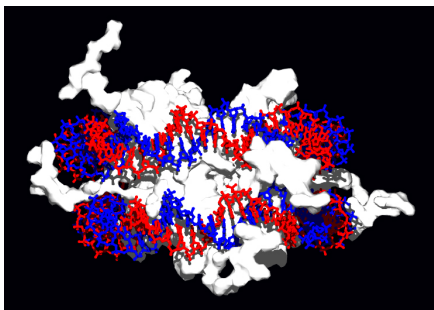
complementary strand by finding the correct base through complementary base pairing, and bonding it onto the original strand. As DNA polymerases can only extend a DNA strand in a 5' to 3' direction, different mechanisms are used to copy the antiparallel strands of the double helix.^[75] In this way, the base on the old strand dictates which base appears on the new strand, and the cell ends up with a perfect copy of its DNA.



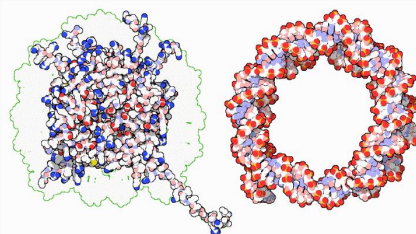
Interactions with proteins

All the functions of DNA depend on interactions with proteins. These protein interactions can be non-specific, or the protein can bind specifically to a single DNA sequence. Enzymes can also bind to DNA and of these, the polymerases that copy the DNA base sequence in transcription and DNA replication are particularly important.

DNA-binding proteins



Interaction of DNA with histones (shown in white, top). These proteins' basic amino acids (below left, blue) bind to the acidic phosphate groups on DNA (below right, red).



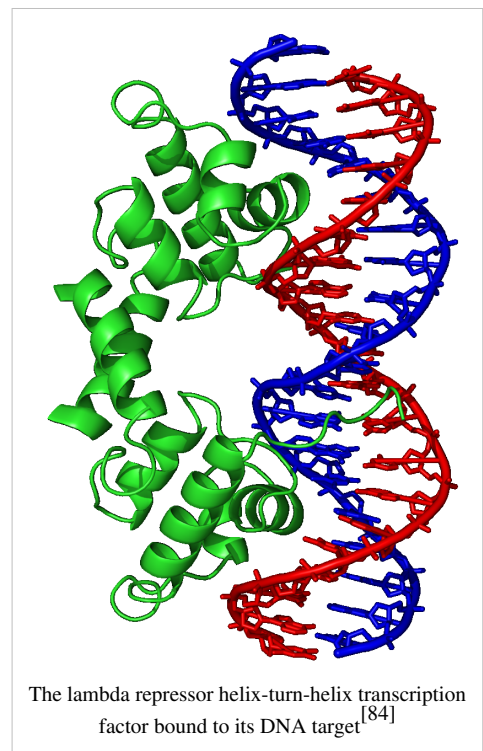
Structural proteins that bind DNA are well-understood examples of non-specific DNA-protein interactions. Within chromosomes, DNA is held in complexes with structural proteins. These proteins organize the DNA into a compact structure called chromatin. In eukaryotes this structure involves DNA binding to a complex of small basic proteins

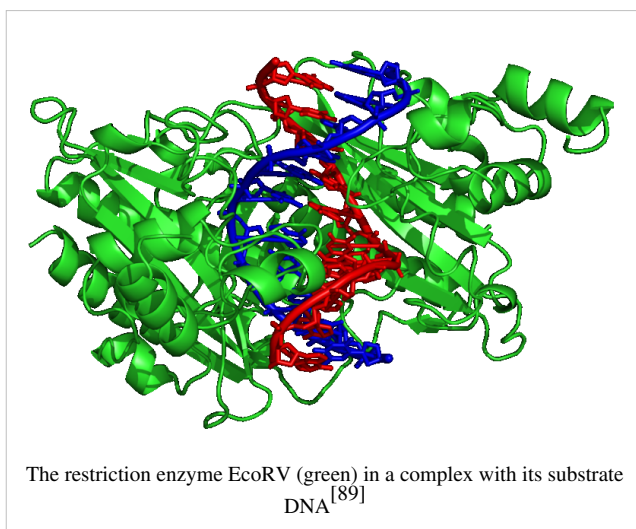
called histones, while in prokaryotes multiple types of proteins are involved.^{[76] [77]} The histones form a disk-shaped complex called a nucleosome, which contains two complete turns of double-stranded DNA wrapped around its surface. These non-specific interactions are formed through basic residues in the histones making ionic bonds to the acidic sugar-phosphate backbone of the DNA, and are therefore largely independent of the base sequence.^[78] Chemical modifications of these basic amino acid residues include methylation, phosphorylation and acetylation.^[79] These chemical changes alter the strength of the interaction between the DNA and the histones, making the DNA more or less accessible to transcription factors and changing the rate of transcription.^[80] Other non-specific DNA-binding proteins in chromatin include the high-mobility group proteins, which bind to bent or distorted DNA.^[81] These proteins are important in bending arrays of nucleosomes and arranging them into the larger structures that make up chromosomes.^[82]

A distinct group of DNA-binding proteins are the DNA-binding proteins that specifically bind single-stranded DNA. In humans, replication protein A is the best-understood member of this family and is used in processes where the double helix is separated, including DNA replication, recombination and DNA repair.^[83] These binding proteins seem to stabilize single-stranded DNA and protect it from forming stem-loops or being degraded by nucleases.

In contrast, other proteins have evolved to bind to particular DNA sequences. The most intensively studied of these are the various transcription factors, which are proteins that regulate transcription. Each transcription factor binds to one particular set of DNA sequences and activates or inhibits the transcription of genes that have these sequences close to their promoters. The transcription factors do this in two ways. Firstly, they can bind the RNA polymerase responsible for transcription, either directly or through other mediator proteins; this locates the polymerase at the promoter and allows it to begin transcription.^[85] Alternatively, transcription factors can bind enzymes that modify the histones at the promoter; this will change the accessibility of the DNA template to the polymerase.^[86]

As these DNA targets can occur throughout an organism's genome, changes in the activity of one type of transcription factor can affect thousands of genes.^[87] Consequently, these proteins are often the targets of the signal transduction processes that control responses to environmental changes or cellular differentiation and development. The specificity of these transcription factors' interactions with DNA come from the proteins making multiple contacts to the edges of the DNA bases, allowing them to "read" the DNA sequence. Most of these base-interactions are made in the major groove, where the bases are most accessible.^[88]





DNA-modifying enzymes

Nucleases and ligases

Nucleases are enzymes that cut DNA strands by catalyzing the hydrolysis of the phosphodiester bonds. Nucleases that hydrolyse nucleotides from the ends of DNA strands are called exonucleases, while endonucleases cut within strands. The most frequently used nucleases in molecular biology are the restriction endonucleases, which cut DNA at specific sequences. For instance, the EcoRV enzyme shown to the left recognizes the 6-base sequence 5'-GAT|ATC-3' and makes a cut at the vertical line. In nature, these enzymes protect bacteria against phage infection by

digesting the phage DNA when it enters the bacterial cell, acting as part of the restriction modification system.^[90] In technology, these sequence-specific nucleases are used in molecular cloning and DNA fingerprinting.

Enzymes called DNA ligases can rejoin cut or broken DNA strands.^[91] Ligases are particularly important in lagging strand DNA replication, as they join together the short segments of DNA produced at the replication fork into a complete copy of the DNA template. They are also used in DNA repair and genetic recombination.^[91]

Topoisomerases and helicases

Topoisomerases are enzymes with both nuclease and ligase activity. These proteins change the amount of supercoiling in DNA. Some of these enzymes work by cutting the DNA helix and allowing one section to rotate, thereby reducing its level of supercoiling; the enzyme then seals the DNA break.^[27] Other types of these enzymes are capable of cutting one DNA helix and then passing a second strand of DNA through this break, before rejoining the helix.^[92] Topoisomerases are required for many processes involving DNA, such as DNA replication and transcription.^[28]

Helicases are proteins that are a type of molecular motor. They use the chemical energy in nucleoside triphosphates, predominantly ATP, to break hydrogen bonds between bases and unwind the DNA double helix into single strands.^[93] These enzymes are essential for most processes where enzymes need to access the DNA bases.

Polymerases

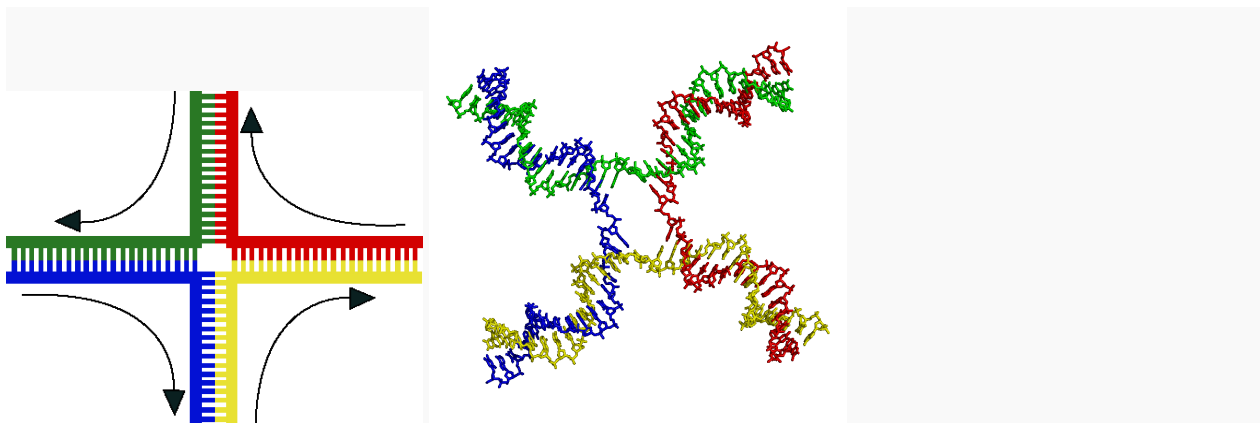
Polymerases are enzymes that synthesize polynucleotide chains from nucleoside triphosphates. The sequence of their products are copies of existing polynucleotide chains - which are called *templates*. These enzymes function by adding nucleotides onto the 3' hydroxyl group of the previous nucleotide in a DNA strand. As a consequence, all polymerases work in a 5' to 3' direction.^[94] In the active site of these enzymes, the incoming nucleoside triphosphate base-pairs to the template: this allows polymerases to accurately synthesize the complementary strand of their template. Polymerases are classified according to the type of template that they use.

In DNA replication, a DNA-dependent DNA polymerase makes a copy of a DNA sequence. Accuracy is vital in this process, so many of these polymerases have a proofreading activity. Here, the polymerase recognizes the occasional mistakes in the synthesis reaction by the lack of base pairing between the mismatched nucleotides. If a mismatch is detected, a 3' to 5' exonuclease activity is activated and the incorrect base removed.^[95] In most organisms, DNA polymerases function in a large complex called the replisome that contains multiple accessory subunits, such as the DNA clamp or helicases.^[96]

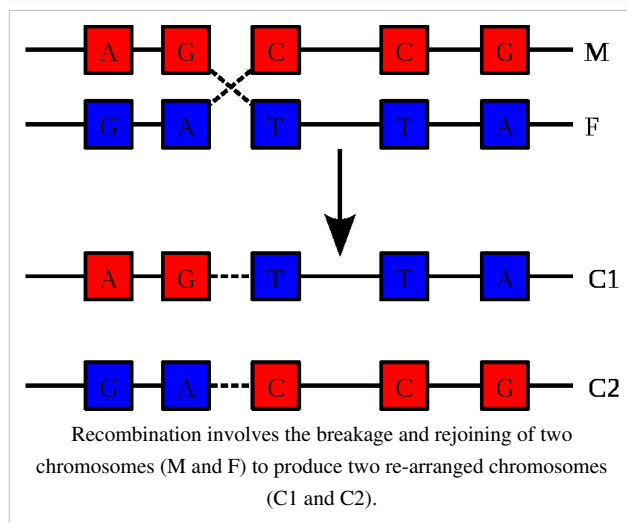
RNA-dependent DNA polymerases are a specialized class of polymerases that copy the sequence of an RNA strand into DNA. They include reverse transcriptase, which is a viral enzyme involved in the infection of cells by retroviruses, and telomerase, which is required for the replication of telomeres.^{[43] [97]} Telomerase is an unusual polymerase because it contains its own RNA template as part of its structure.^[44]

Transcription is carried out by a DNA-dependent RNA polymerase that copies the sequence of a DNA strand into RNA. To begin transcribing a gene, the RNA polymerase binds to a sequence of DNA called a promoter and separates the DNA strands. It then copies the gene sequence into a messenger RNA transcript until it reaches a region of DNA called the terminator, where it halts and detaches from the DNA. As with human DNA-dependent DNA polymerases, RNA polymerase II, the enzyme that transcribes most of the genes in the human genome, operates as part of a large protein complex with multiple regulatory and accessory subunits.^[98]

Genetic recombination



Structure of the Holliday junction intermediate in genetic recombination. The four separate DNA strands are coloured red, blue, green and yellow.^[99]



of the two helices by at least one Holliday junction, in which a segment of a single strand in each helix is annealed to the complementary strand in the other helix. The Holliday junction is a tetrahedral junction structure that can be moved along the pair of chromosomes, swapping one strand for another. The recombination reaction is then halted by cleavage of the junction and re-ligation of the released DNA.^[105]

Evolution

DNA contains the genetic information that allows all modern living things to function, grow and reproduce. However, it is unclear how long in the 4-billion-year history of life DNA has performed this function, as it has been proposed that the earliest forms of life may have used RNA as their genetic material.^{[94] [106]} RNA may have acted as the central part of early cell metabolism as it can both transmit genetic information and carry out catalysis as part of ribozymes.^[107] This ancient RNA world where nucleic acid would have been used for both catalysis and genetics may have influenced the evolution of the current genetic code based on four nucleotide bases. This would occur, since the number of different bases in such an organism is a trade-off between a small number of bases increasing replication accuracy and a large number of bases increasing the catalytic efficiency of ribozymes.^[108]

However, there is no direct evidence of ancient genetic systems, as recovery of DNA from most fossils is impossible. This is because DNA will survive in the environment for less than one million years and slowly degrades into short fragments in solution.^[109] Claims for older DNA have been made, most notably a report of the isolation of a viable bacterium from a salt crystal 250 million years old,^[110] but these claims are controversial.^{[111] [112]}

Uses in technology

Genetic engineering

Genetic engineering, also called genetic modification, is the direct human manipulation of an organism's genetic material in a way that does not occur under natural conditions. It involves the use of recombinant DNA techniques, but does not include traditional animal and plant breeding or mutagenesis. Any organism that is generated using these techniques is considered to be a genetically modified organism. The first organisms genetically engineered were bacteria in 1973 and then mice in 1974. Insulin producing bacteria were commercialized in 1982 and genetically modified food has been sold since 1994.

Producing genetically modified organisms or tissues is a multi-step process. It first involves the isolating and copying the genetic material of interest; if necessary, changes to genetic sequence may be introduced. A construct may be built containing all the genetic elements for correct expression in a vector. This vector construct is then introduced into the host organism in a process called transformation, transfection or transduction. Successfully transformed organisms or tissues are then selectively grown, usually by growing material in conditions which require the presence of a gene in the inserted material for survival.

Genetic engineering techniques have been applied to various industries, with some success. Medicines such as insulin and human growth hormone are now produced in bacteria, experimental mice such as the oncomouse and the knockout mouse are being used for research purposes and insect resistant and/or herbicide tolerant crops have been commercialized. Plants that contain drugs and vaccines, animals with beneficial proteins in their milk and stress tolerant crops are currently being developed.

Forensics

Forensic scientists can use DNA in blood, semen, skin, saliva or hair found at a crime scene to identify a matching DNA of an individual, such as a perpetrator. This process is formally termed DNA profiling, but may also be called "genetic fingerprinting". In DNA profiling, the lengths of variable sections of repetitive DNA, such as short tandem repeats and minisatellites, are compared between people. This method is usually an extremely reliable technique for identifying a matching DNA.^[113] However, identification can be complicated if the scene is contaminated with DNA from several people.^[114] DNA profiling was developed in 1984 by British geneticist Sir Alec Jeffreys,^[115] and first used in forensic science to convict Colin Pitchfork in the 1988 Enderby murders case.^[116]

People convicted of certain types of crimes may be required to provide a sample of DNA for a database. This has helped investigators solve old cases where only a DNA sample was obtained from the scene. DNA profiling can also be used to identify victims of mass casualty incidents.^[117] On the other hand, many convicted people have been released from prison on the basis of DNA techniques, which were not available when a crime had originally been committed.

Bioinformatics

Bioinformatics involves the manipulation, searching, and data mining of biological data, and this includes DNA sequence data. The development of techniques to store and search DNA sequences have led to widely applied advances in computer science, especially string searching algorithms, machine learning and database theory.^[118] String searching or matching algorithms, which find an occurrence of a sequence of letters inside a larger sequence of letters, were developed to search for specific sequences of nucleotides.^[119] The DNA sequenced may be aligned with other DNA sequences to identify homologous sequences and locate the specific mutations that make them distinct. These techniques, especially multiple sequence alignment, are used in studying phylogenetic relationships and protein function.^[120] Data sets representing entire genomes' worth of DNA sequences, such as those produced by the Human Genome Project, are difficult to use without the annotations that identify the locations of genes and regulatory elements on each chromosome. Regions of DNA sequence that have the characteristic patterns associated with protein- or RNA-coding genes can be identified by gene finding algorithms, which allow researchers to predict the presence of particular gene products and their possible functions in an organism even before they have been isolated experimentally.^[121] Entire genomes may also be compared which can shed light on the evolutionary history of particular organism and permit the examination of complex evolutionary events.

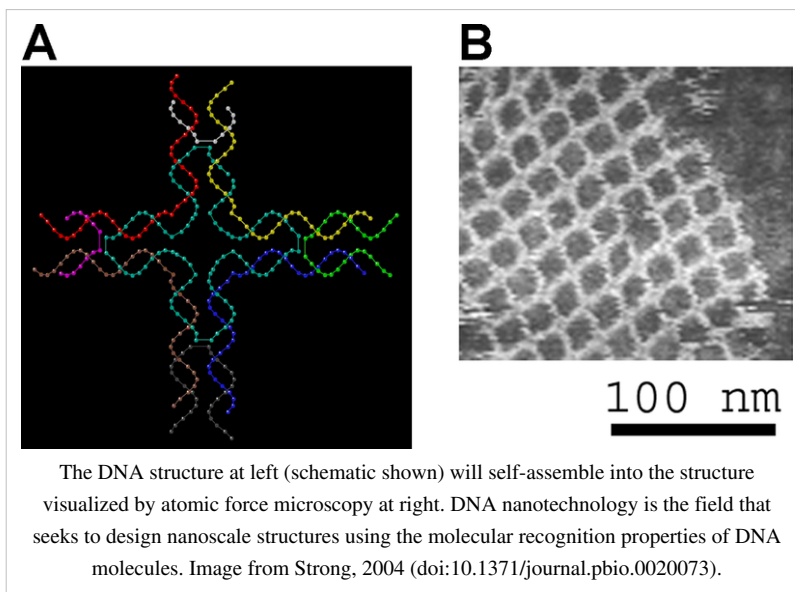
DNA nanotechnology

DNA nanotechnology uses the unique molecular recognition properties of DNA and other nucleic acids to create self-assembling branched DNA complexes with useful properties.^[122]

DNA is thus used as a structural material rather than as a carrier of biological information. This has led to the creation of two-dimensional periodic lattices (both tile-based as well as using the "DNA origami" method) as well as three-dimensional structures in the shapes of polyhedra.^[123]

Nanomechanical devices and algorithmic self-assembly have also been demonstrated,^[124] and

these DNA structures have been used to template the arrangement of other molecules such as gold nanoparticles and streptavidin proteins.^[125]



History and anthropology

Because DNA collects mutations over time, which are then inherited, it contains historical information, and, by comparing DNA sequences, geneticists can infer the evolutionary history of organisms, their phylogeny.^[126] This field of phylogenetics is a powerful tool in evolutionary biology. If DNA sequences within a species are compared, population geneticists can learn the history of particular populations. This can be used in studies ranging from ecological genetics to anthropology; For example, DNA evidence is being used to try to identify the Ten Lost Tribes of Israel.^{[127] [128]}

DNA has also been used to look at modern family relationships, such as establishing family relationships between the descendants of Sally Hemings and Thomas Jefferson. This usage is closely related to the use of DNA in criminal investigations detailed above. Indeed, some criminal investigations have been solved when DNA from crime scenes has matched relatives of the guilty individual.^[129]

History of DNA research

DNA was first isolated by the Swiss physician Friedrich Miescher who, in 1869, discovered a microscopic substance in the pus of discarded surgical bandages. As it resided in the nuclei of cells, he called it "nuclein".^[130] In 1919, Phoebus Levene identified the base, sugar and phosphate nucleotide unit.^[131] Levene suggested that DNA consisted of a string of nucleotide units linked together through the phosphate groups. However, Levene thought the chain was short and the bases repeated in a fixed order. In 1937 William Astbury produced the first X-ray diffraction patterns that showed that DNA had a regular structure.^[132]

In 1928, Frederick Griffith discovered that traits of the "smooth" form of the *Pneumococcus* could be transferred to the "rough" form of the same bacteria by mixing killed "smooth" bacteria with the live "rough" form.^[133] This system provided the first clear suggestion that DNA carries genetic information—the

Avery–MacLeod–McCarty experiment—when Oswald Avery, along with coworkers Colin MacLeod and Maclyn McCarty, identified DNA as the transforming principle in 1943.^[134] DNA's role in heredity was confirmed in 1952, when Alfred Hershey and Martha Chase in the Hershey–Chase experiment showed that DNA is the genetic material of the T2 phage.^[135]

In 1953, James D. Watson and Francis Crick suggested what is now accepted as the first correct double-helix model of DNA structure in the journal



James D. Watson and Francis Crick (right), co-originators of the double-helix model, with Maclyn McCarty (left).



Rosalind Franklin, co-creator of the single X-ray diffraction image



Raymond Gosling, co-creator of the single X-ray diffraction image

Nature.^[5] Their double-helix, molecular model of DNA was then based on a single X-ray diffraction image (labeled as "Photo 51")^[136] taken by Rosalind Franklin and Raymond Gosling in May 1952, as well as the information that the DNA bases are paired — also obtained through private communications from Erwin Chargaff in the previous years. Chargaff's rules played a very important role in establishing double-helix configurations for B-DNA as well as A-DNA.

Experimental evidence supporting the Watson and Crick model were published in a series of five articles in the same issue of *Nature*.^[137] Of these, Franklin and Gosling's paper was the first publication of their own X-ray diffraction data and original analysis method that partially supported the Watson and Crick model;^[31] ^[138] this issue also contained an article on DNA structure by Maurice Wilkins and two of his colleagues, whose analysis and *in vivo* B-DNA X-ray patterns also supported the presence *in vivo* of the double-helical DNA configurations as proposed by Crick and Watson for their double-helix molecular model of DNA in the previous two pages of *Nature*.^[32] In 1962, after

Franklin's death, Watson, Crick, and Wilkins jointly received the Nobel Prize in Physiology or Medicine.^[139] However, Nobel rules of the time allowed only living recipients, but a vigorous debate continues on who should receive credit for the discovery.^[140]

In an influential presentation in 1957, Crick laid out the central dogma of molecular biology, which foretold the relationship between DNA, RNA, and proteins, and articulated the "adaptor hypothesis".^[141] Final confirmation of the replication mechanism that was implied by the double-helical structure followed in 1958 through the Meselson–Stahl experiment.^[142] Further work by Crick and coworkers showed that the genetic code was based on non-overlapping triplets of bases, called codons, allowing Har Gobind Khorana, Robert W. Holley and Marshall Warren Nirenberg to decipher the genetic code.^[143] These findings represent the birth of molecular biology.

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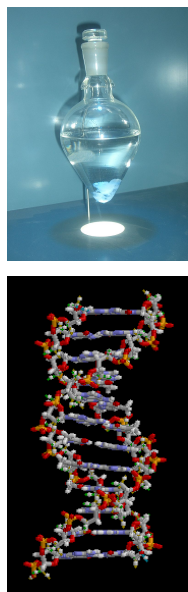
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External links

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- DNA binding site prediction on protein (<http://pipe.scs.fsu.edu/displar.html>)
- DNA coiling to form chromosomes (http://biostudio.com/c_education_mac.htm)
- DNA from the Beginning (<http://www.dnafb.org/dnafb/>) Another DNA Learning Center site on DNA, genes, and heredity from Mendel to the human genome project.
- DNA Lab, demonstrates how to extract DNA from wheat using readily available equipment and supplies. (<http://ca.youtube.com/watch?v=iyb7fwduuGM>)
- DNA the Double Helix Game (http://nobelprize.org/educational_games/medicine/dna_double_helix/) From the official Nobel Prize web site
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- The Register of Francis Crick Personal Papers 1938 - 2007 (<http://orpheus.ucsd.edu/speccoll/testing/html/mss0660a.html#abstract>) at Mandeville Special Collections Library, Geisel Library, University of California, San Diego
- U.S. National DNA Day (<http://www.genome.gov/10506367>)—watch videos and participate in real-time chat with top scientists
- "Clue to chemistry of heredity found" (<http://www.nytimes.com/packages/pdf/science/dna-article.pdf>). *The New York Times*. Saturday, June 13, 1953. The first American newspaper coverage of the discovery of the DNA structure.
- An Introduction to DNA and Chromosomes (<http://hopes.stanford.edu/basics/dna/b0.html>) from HOPES: Huntington's Disease Outreach Project for Education at Stanford

Molecular models of DNA



Molecular models of DNA structures are representations of the molecular geometry and topology of Deoxyribonucleic acid (DNA) molecules using one of several means, with the aim of simplifying and presenting the essential, physical and chemical, properties of DNA molecular structures either *in vivo* or *in vitro*. These representations include closely packed spheres (CPK models) made of plastic, metal wires for 'skeletal models', graphic computations and animations by computers, artistic rendering. Computer molecular models also allow animations and molecular dynamics simulations that are very important for understanding how DNA functions *in vivo*.

The more advanced, computer-based molecular models of DNA involve molecular dynamics simulations as well as quantum mechanical computations of vibro-rotations, delocalized molecular orbitals (MOs), electric dipole moments, hydrogen-bonding, and so on. **DNA molecular dynamics modeling** involves simulations of DNA molecular geometry and topology changes with time as a result of both intra- and inter- molecular interactions of DNA. Whereas molecular models of Deoxyribonucleic acid (DNA) molecules such as closely packed spheres (CPK models) made of plastic or metal wires for 'skeletal models' are useful representations of static DNA structures, their usefulness is very limited for representing complex DNA dynamics. Computer molecular modeling allows both animations and molecular dynamics simulations that are very important for understanding how DNA functions *in vivo*.

History



The A-DNA double-helix molecular model of Crick and Watson (consistent with their X-ray data) for which they received a Nobel prize together with M.H.F. Wilkins.

From the very early stages of structural studies of DNA by X-ray diffraction and biochemical means, molecular models such as the Watson-Crick double-helix model were successfully employed to solve the 'puzzle' of DNA structure, and also find how the latter relates to its key functions in living cells. The first high quality X-ray diffraction patterns of A-DNA were reported by Rosalind Franklin and Raymond Gosling in 1953^[1]. The first calculations of the Fourier transform of an atomic helix were reported one year earlier by Cochran, Crick and Vand^[2], and were followed in 1953 by the computation of the Fourier transform of a coiled-coil by Crick^[3].

Structural information is generated from X-ray diffraction studies of oriented DNA fibers with the help of molecular models of DNA that are combined with crystallographic and mathematical analysis of the X-ray patterns.

The first reports of a double-helix molecular model of B-DNA structure were made by Watson and Crick in 1953^[4] ^[5]. Last-but-not-least, Maurice F. Wilkins, A. Stokes and H.R. Wilson, reported the first X-ray patterns of *in vivo* B-DNA in partially oriented salmon sperm heads^[6]. The development of the first correct double-helix molecular model of DNA by Crick and

Watson may not have been possible without the biochemical evidence for the nucleotide base-pairing ([A---T]; [C---G]), or Chargaff's rules^[7] ^[8] ^[9] ^[10] ^[11] ^[12]. Although such initial studies of DNA structures with the help of molecular models were essentially static, their consequences for explaining the *in vivo* functions of DNA were significant in the areas of protein biosynthesis and the quasi-universality of the genetic code. Epigenetic transformation studies of DNA *in vivo* were however much slower to develop in spite of their importance for embryology, morphogenesis and cancer research. Such chemical dynamics and biochemical reactions of DNA are much more complex than the molecular dynamics of DNA physical interactions with water, ions and proteins/enzymes in living cells.

Importance

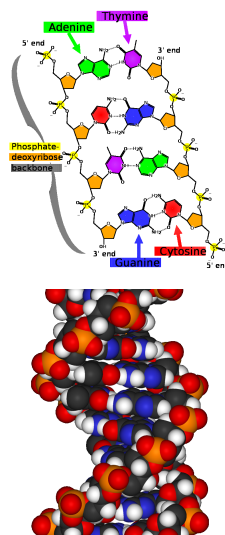
An old standing dynamic problem is how DNA "self-replication" takes place in living cells that should involve transient uncoiling of supercoiled DNA fibers. Although DNA consists of relatively rigid, very large elongated biopolymer molecules called "fibers" or chains (that are made of repeating nucleotide units of four basic types, attached to deoxyribose and phosphate groups), its molecular structure *in vivo* undergoes dynamic configuration changes that involve dynamically attached water molecules and ions. Supercoiling, packing with histones in chromosome structures, and other such supramolecular aspects also involve *in vivo* DNA topology which is even more complex than DNA molecular geometry, thus turning molecular modeling of DNA into an especially challenging problem for both molecular biologists and biotechnologists. Like other large molecules and biopolymers, DNA often exists in multiple stable geometries (that is, it exhibits conformational isomerism) and configurational, quantum states which are close to each other in energy on the potential energy surface of the DNA molecule.

Such varying molecular geometries can also be computed, at least in principle, by employing *ab initio* quantum chemistry methods that can attain high accuracy for small molecules, although claims that acceptable accuracy can be also achieved for polynucleotides, as well as DNA conformations, were recently made on the basis of VCD spectral data. Such quantum geometries define an important class of *ab initio* molecular models of DNA whose exploration has barely started especially in connection with results obtained by VCD in solutions. More detailed comparisons with such *ab initio* quantum computations are in principle obtainable through 2D-FT NMR spectroscopy and relaxation studies of polynucleotide solutions or specifically labeled DNA, as for example with

deuterium labels.

In an interesting twist of roles, the DNA molecule itself was proposed to be utilized for quantum computing. Both DNA nanostructures as well as DNA 'computing' biochips have been built.

Fundamental concepts



The chemical structure of DNA is insufficient to understand the complexity of the 3D structures of DNA. On the other hand, animated molecular models allow one to visually explore the three-dimensional (3D) structure of DNA. The DNA model shown (far right) is a space-filling, or CPK, model of the DNA double-helix. Animated molecular models, such as the wire, or skeletal, type shown at the top of this article, allow one to visually explore the three-dimensional (3D) structure of DNA. Another type of DNA model is the space-filling, or CPK, model.

The hydrogen bonding dynamics and proton exchange is very different by many orders of magnitude between the two systems of fully hydrated DNA and water molecules in ice. Thus, the DNA dynamics is complex, involving nanosecond and several tens of picosecond time scales, whereas that of liquid ice is on the picosecond time scale, and that of proton exchange in ice is on the millisecond time scale. The proton exchange rates in DNA and attached proteins may vary from picosecond to nanosecond, minutes or years, depending on the exact locations of the exchanged protons in the large biopolymers.

A simple harmonic oscillator 'vibration' is only an oversimplified dynamic representation of the longitudinal vibrations of the DNA intertwined helices which were found to be anharmonic rather than harmonic as often assumed in quantum dynamic simulations of DNA.

DNA structure

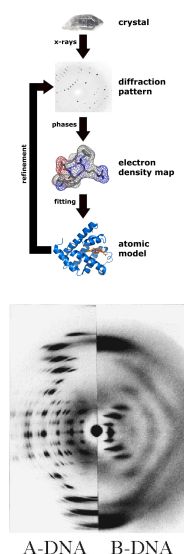
The structure of DNA shows a variety of forms, both double-stranded and single-stranded. The mechanical properties of DNA, which are directly related to its structure, are a significant problem for cells. Every process which binds or reads DNA is able to use or modify the mechanical properties of DNA for purposes of recognition, packaging and modification. The extreme length (a chromosome may contain a 10 cm long DNA strand), relative rigidity and helical structure of DNA has led to the evolution of histones and of enzymes such as topoisomerases and helicases to manage a cell's DNA. The properties of DNA are closely related to its molecular structure and sequence, particularly the weakness of the hydrogen bonds and electronic interactions that hold strands of DNA together compared to the strength of the bonds within each strand.

Experimental techniques which can directly measure the mechanical properties of DNA are relatively new, and high-resolution visualization in solution is often difficult. Nevertheless, scientists have uncovered large amount of

data on the mechanical properties of this polymer, and the implications of DNA's mechanical properties on cellular processes is a topic of active current research.

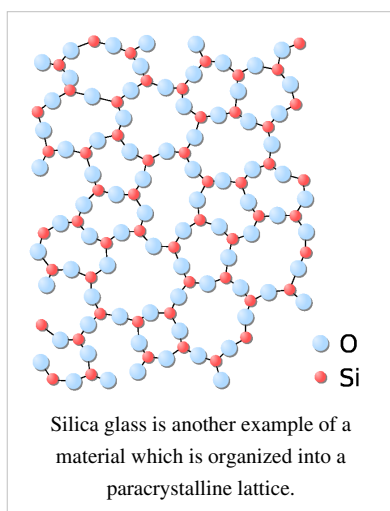
The DNA found in many cells can be macroscopic in length - a few centimetres long for each human chromosome. Consequently, cells must compact or "package" DNA to carry it within them. In eukaryotes this is carried by spool-like proteins known as histones, around which DNA winds. It is the further compaction of this DNA-protein complex which produces the well known mitotic eukaryotic chromosomes.

DNA structure determination using molecular modeling and DNA X-ray patterns



After DNA has been separated and purified by standard biochemical techniques one has a sample in a jar much like in the figure at the top of this article. Below are the main steps involved in generating structural information from X-ray diffraction studies of oriented DNA fibers that are drawn from the hydrated DNA sample with the help of molecular models of DNA that are combined with crystallographic and mathematical analysis of the X-ray patterns.

Paracrystalline lattice models of B-DNA structures



A paracrystalline lattice, or paracrystal, is a molecular or atomic lattice with significant amounts (e.g., larger than a few percent) of partial disordering of molecular arrangements. Limiting cases of the paracrystal model are nanostructures, such as glasses, liquids, etc., that may possess only local ordering and no global order. A simple example of a paracrystalline lattice is shown in the following figure for a silica glass:

Liquid crystals also have paracrystalline rather than crystalline structures.

Highly hydrated B-DNA occurs naturally in living cells in such a paracrystalline state, which is a dynamic one in spite of the relatively rigid DNA double-helix stabilized by parallel hydrogen bonds between the nucleotide base-pairs in the two complementary, helical DNA chains (see figures). For simplicity most DNA molecular models omit both water and ions dynamically bound to B-DNA, and are thus less useful for understanding

the dynamic behaviors of B-DNA *in vivo*. The physical and mathematical analysis of X-ray^{[13] [14]} and spectroscopic data for paracrystalline B-DNA is therefore much more complicated than that of crystalline, A-DNA X-ray diffraction patterns. The paracrystal model is also important for DNA technological applications such as DNA nanotechnology. Novel techniques that combine X-ray diffraction of DNA with X-ray microscopy in hydrated living cells are now also being developed.^[15]

Genomic and biotechnology applications of DNA molecular modeling

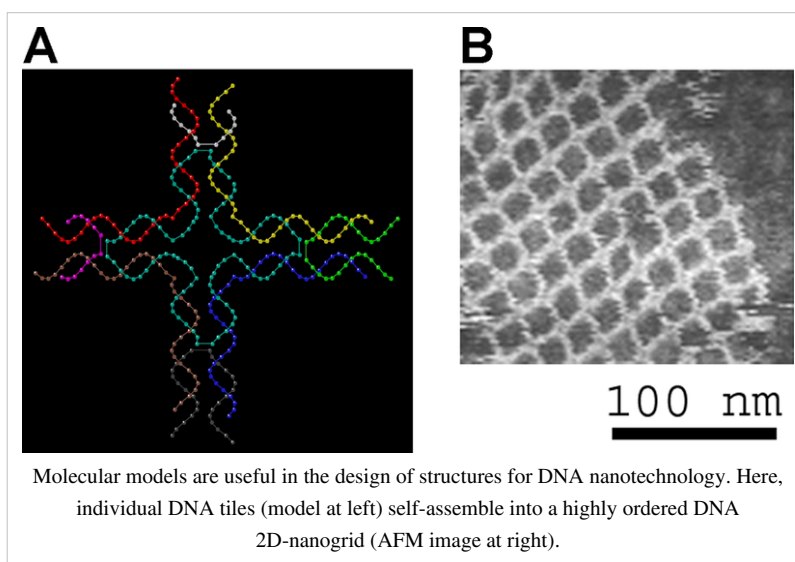
There are various uses of DNA molecular modeling in Genomics and Biotechnology research applications, from DNA repair to PCR and DNA nanostructures. Two-dimensional DNA junction arrays have been visualized by Atomic force microscopy.^[16]

DNA molecular modeling has various uses in genomics and biotechnology, with research applications ranging from DNA repair to PCR and DNA nanostructures. These include computer molecular models of molecules as varied as RNA polymerase, an *E. coli*, bacterial DNA

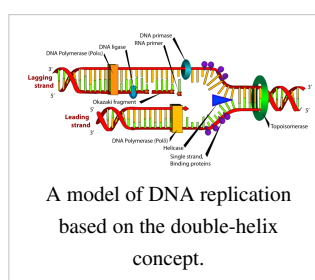
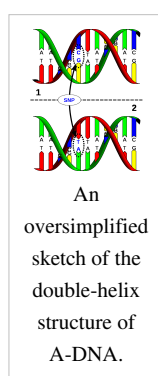
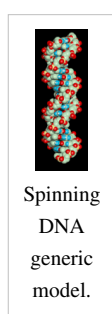
primase template suggesting very complex dynamics at the interfaces between the enzymes and the DNA template, and molecular models of the mutagenic, chemical interaction of potent carcinogen molecules with DNA. These are all represented in the gallery below.

Technological application include a DNA biochip and DNA nanostructures designed for DNA computing and other dynamic applications of DNA nanotechnology.^{[17] [18] [19] [20] [21] [22]} The image at right is of self-assembled DNA nanostructures. The DNA “tile” structure in this image consists of four branched junctions oriented at 90° angles. Each tile consists of nine DNA oligonucleotides as shown; such tiles serve as the primary “building block” for the assembly of the DNA nanogrids shown in the AFM micrograph.

Quadruplex DNA^[23] may be involved in certain cancers.^{[24] [25]} Images of quadruplex DNA are in the gallery below.

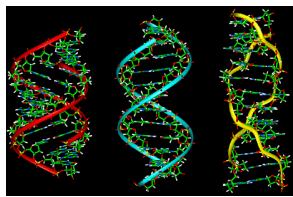


Gallery of DNA models

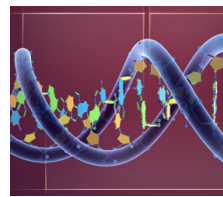




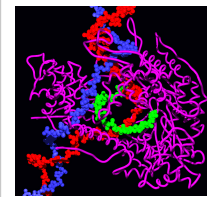
A large-scale
Crick-Watson
DNA Model
shown in the
Museum of
Príncipe Felipe.



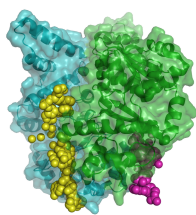
Side view of molecular models of
A- , B-, Z- DNA.



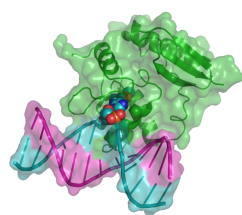
Oversimplified model of
the A-DNA double-helix.



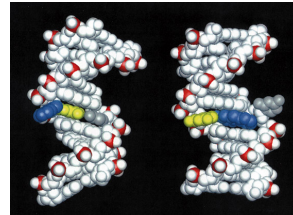
Molecular modeling of
RNA Polymerase.



Molecular modeling of
a bacterial DNA
Primase Template.



Molecular modeling of DNA
interactions with the
carcinogen molecule MGMT.



3D Molecular model of DNA
damaged by carcinogenic
2-aminofluorene (AF).

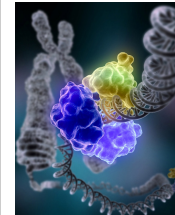
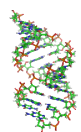
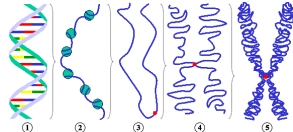


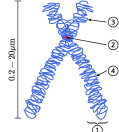
Fig.6. Molecular
modeling of DNA
repair



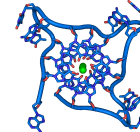
Animated
skeletal
model of
A-DNA.



Simplified models of chromatin.



Simplified
model of
chromosome
structure.



A hypothetical
quadruplex of
guanine-rich
DNA structures
that may be
involved in
cancers.



3D Molecular
Structure of
the
intramolecular
human
telomeric
G-quadruplex
in potassium
solution.



DNA spacefilling molecular
model



A model of
a designed
DNA
tetrahedron.

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Further reading

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External links

- DNA the Double Helix Game (http://nobelprize.org/educational_games/medicine/dna_double_helix/) From the official Nobel Prize web site
- MDDNA: Structural Bioinformatics of DNA (<http://humphry.chem.wesleyan.edu:8080/MDDNA/>)
- Double Helix 1953–2003 (<http://www.ncbe.reading.ac.uk/DNA50/>) National Centre for Biotechnology Education
- DNALive: a web interface to compute DNA physical properties (<http://mmb.pcb.ub.es/DNALive>). Also allows cross-linking of the results with the UCSC Genome browser and DNA dynamics.
- DiProDB: Dinucleotide Property Database (<http://diprodb.fli-leibniz.de>). The database is designed to collect and analyse thermodynamic, structural and other dinucleotide properties.
- Further details of mathematical and molecular analysis of DNA structure based on X-ray data (<http://planetphysics.org/encyclopedia/BesselFunctionsApplicationsToDiffractionByHelicalStructures.html>)
- Bessel functions corresponding to Fourier transforms of atomic or molecular helices. (<http://planetphysics.org/?op=getobj&from=objects&name=BesselFunctionsAndTheirApplicationsToDiffractionByHelicalStructures>)
- overview of STM/AFM/SNOM principles with educative videos (<http://www.ntmdt.ru/SPM-Techniques/Principles/>)

Databases for DNA molecular models and sequences

X-ray diffraction

- NDB ID: UD0017 Database (<http://ndbserver.rutgers.edu/atlas/xray/structures/U/ud0017/ud0017.html>)
- X-ray Atlas -database (<http://ndbserver.rutgers.edu/atlas/xray/index.html>)
- PDB files of coordinates for nucleic acid structures from X-ray diffraction by NA (incl. DNA) crystals (<http://ndbserver.rutgers.edu/ftp/NDB/coordinates/na-biol/>)
- Structure factors downloadable files in CIF format (<http://ndbserver.rutgers.edu/ftp/NDB/structure-factors/>)

Neutron scattering

- ISIS neutron source: ISIS pulsed neutron source: A world centre for science with neutrons & muons at Harwell, near Oxford, UK. (<http://www.isis.rl.ac.uk/>)

X-ray microscopy

Electron microscopy

- DNA under electron microscope (http://www.fidelitysystems.com/Unlinked_DNA.html)

NMR databases

- NMR Atlas--database (<http://ndbserver.rutgers.edu/atlas/nmr/index.html>)
- mmCIF downloadable coordinate files of nucleic acids in solution from 2D-FT NMR data (<http://ndbserver.rutgers.edu/ftp/NDB/coordinates/na-nmr-mmCIF/>)
- NMR constraints files for NAs in PDB format (<http://ndbserver.rutgers.edu/ftp/NDB/nmr-restraints/>)

Genomic and structural databases

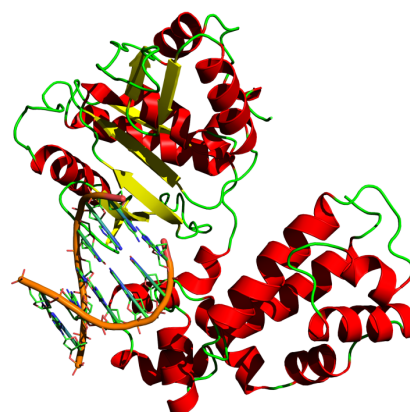
- CBS Genome Atlas Database (<http://www.cbs.dtu.dk/services/GenomeAtlas/>) — contains examples of base skews.
- The Z curve database of genomes — a 3-dimensional visualization and analysis tool of genomes (<http://tubic.tju.edu.cn/zcurve/>).
- DNA and other nucleic acids' molecular models: Coordinate files of nucleic acids molecular structure models in PDB and CIF formats (<http://ndbserver.rutgers.edu/ftp/NDB/models/>)

Atomic force microscopy

- How SPM Works (http://www.parkafm.com/New_html/resources/01general.php)
- SPM Image Gallery - AFM STM SEM MFM NSOM and more. (<http://www.rhk-tech.com/results/showcase.php>)

DNA polymerase

A **DNA polymerase** is an enzyme that catalyzes the polymerization of deoxyribonucleotides into a DNA strand. DNA polymerases are best-known for their feedback role in DNA replication, in which the polymerase "reads" an intact DNA strand as a template and uses it to synthesize the new strand. This process copies a piece of DNA. The newly-polymerized molecule is complementary to the template strand and identical to the template's original partner strand. DNA polymerases use magnesium ions as cofactors. Human DNA polymerases are 900-1000 amino acids long.



3D structure of the DNA-binding helix-turn-helix motifs in human DNA polymerase beta

Function

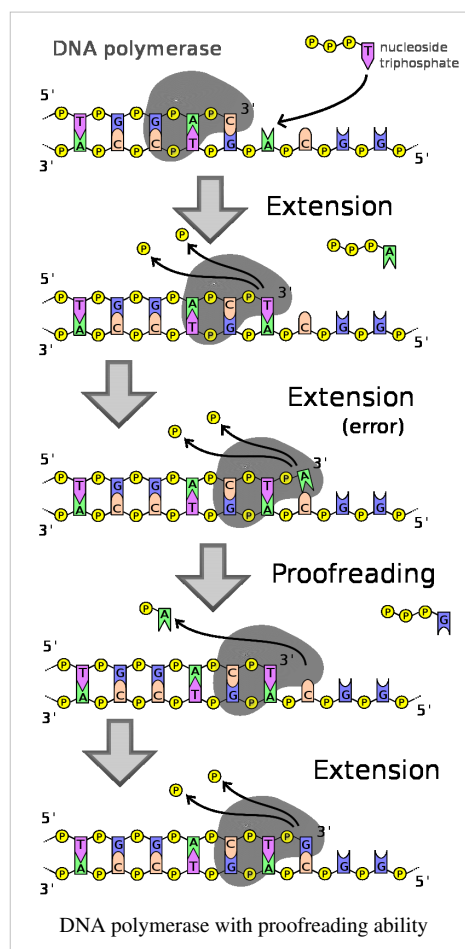
DNA polymerase can add free nucleotides to only the 3' end of the newly-forming strand. This results in elongation of the new strand in a 5'-3' direction. No known DNA polymerase is able to begin a new chain (*de novo*). DNA polymerase can add a nucleotide onto only a preexisting 3'-OH group, and, therefore, needs a primer at which it can add the first nucleotide. Primers consist of RNA and/or DNA bases. In DNA replication, the first two bases are always RNA, and are synthesized by another enzyme called primase. An enzyme known as a helicase is required to unwind DNA from a double-strand structure to a single-strand structure to facilitate replication of each strand consistent with the semiconservative model of DNA replication.

Error correction is a property of some, but not all, DNA polymerases. This process corrects mistakes in newly-synthesized DNA. When an incorrect base pair is recognized, DNA polymerase reverses its direction by one base pair of DNA. The 3'-5' exonuclease activity of the enzyme allows the incorrect base pair to be excised (this activity is known as *proofreading*). Following base excision, the polymerase can re-insert the correct base and replication can continue.

Various DNA polymerases are extensively used in molecular biology experiments.

Variation across species

DNA polymerases have highly-conserved structure, which means that their overall catalytic subunits vary, on a whole, very little from species to species. Conserved structures usually indicate important, irreplaceable functions of the cell, the maintenance of which provides evolutionary advantages.



Some viruses also encode special DNA polymerases, such as Hepatitis B virus DNA polymerase. These may selectively replicate viral DNA through a variety of mechanisms. Retroviruses encode an unusual DNA polymerase called reverse transcriptase, which is an RNA-dependent DNA polymerase (RdDp). It polymerizes DNA from a template of RNA.

DNA polymerase families

Based on sequence homology, DNA polymerases can be further subdivided into seven different families: A, B, C, D, X, Y, and RT.

Family A

Polymerases contain both replicative and repair polymerases. Replicative members from this family include the extensively-studied T7 DNA polymerase, as well as the eukaryotic mitochondrial DNA Polymerase γ . Among the repair polymerases are *Escherichia coli* DNA pol I, *Thermus aquaticus* pol I, and *Bacillus stearothermophilus* pol I. These repair polymerases are involved in excision repair and processing of Okazaki fragments generated during lagging strand synthesis.

Family C

Polymerases are the primary bacterial chromosomal replicative enzymes. DNA Polymerase III alpha subunit from *E. coli* is the catalytic subunit^[1] and possesses no known nuclease activity. A separate subunit, the epsilon subunit, possesses the 3'-5' exonuclease activity used for editing during chromosomal replication. Recent research has classified Family C polymerases as a subcategory of Family X.

Family D

Polymerases are still not very well characterized. All known examples are found in the Euryarchaeota subdomain of Archaea and are thought to be replicative polymerases.

Family X

Contains the well-known eukaryotic polymerase pol β , as well as other eukaryotic polymerases such as pol σ , pol λ , pol μ , and terminal deoxynucleotidyl transferase (TdT). Pol β is required for short-patch base excision repair, a DNA repair pathway that is essential for repairing abasic sites. Pol λ and Pol μ are involved in non-homologous end-joining, a mechanism for rejoining DNA double-strand breaks. TdT is expressed only in lymphoid tissue, and adds "n nucleotides" to double-strand breaks formed during V(D)J recombination to promote immunological diversity. The yeast *Saccharomyces cerevisiae* has only one Pol X polymerase, Pol IV, which is involved in non-homologous end-joining.

Family Y

Polymerases differ from others in having a low fidelity on undamaged templates and in their ability to replicate through damaged DNA. Members of this family are hence called translesion synthesis (TLS) polymerases. Depending on the lesion, TLS polymerases can bypass the damage in an error-free or error-prone fashion, the latter resulting in elevated mutagenesis. Xeroderma pigmentosum variant (XPV) patients for instance have mutations in the gene encoding Pol η (eta), which is error-free for UV-lesions. In XPV patients, alternative error-prone polymerases, e.g., Pol ζ (zeta) (polymerase ζ is a B Family polymerase a complex of the catalytic subunit REV3L with Rev7, which associates with Rev1^[2]), are thought to be involved in mistakes that result in the cancer predisposition of these patients. Other members in humans are Pol ι (iota), Pol κ (kappa), and Rev1 (terminal deoxycytidyl transferase). In *E. coli*, two TLS polymerases, Pol IV (DINB) and Pol V (UmuD'₂C), are known.

Family RT

The reverse transcriptase family contains examples from both retroviruses and eukaryotic polymerases. The eukaryotic polymerases are usually restricted to telomerases. These polymerases use an RNA template to synthesize the DNA strand.

Prokaryotic DNA polymerases

Bacteria have 5 known DNA polymerases.

Eukaryotic DNA polymerases

Eukaryotes have at least 15 DNA Polymerases.^[3]

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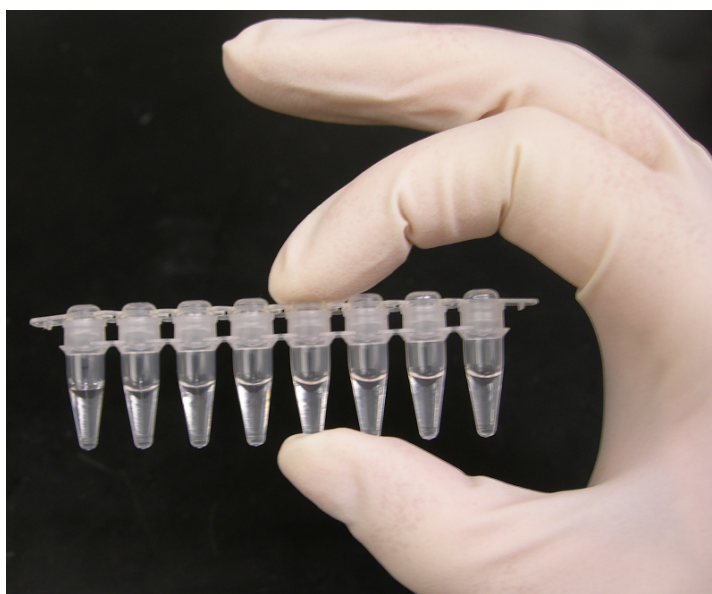
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- EC 2.7.7.7 (<http://www.expasy.org/cgi-bin/nicezyme.pl?2.7.7.7>)
- A great animation of DNA Polymerase from WEHI at 2:55 minutes in (http://www.perimeterinstitute.ca/en/Outreach/Public_Lectures/View_Past_Public_Lectures/)

Polymerase chain reaction

The **polymerase chain reaction (PCR)** is a scientific technique in molecular biology to amplify a single or a few copies of a piece of DNA across several orders of magnitude, generating thousands to millions of copies of a particular DNA sequence. The method relies on thermal cycling, consisting of cycles of repeated heating and cooling of the reaction for DNA melting and enzymatic replication of the DNA. Primers (short DNA fragments) containing sequences complementary to the target region along with a DNA polymerase (after which the method is named) are key components to enable selective and repeated amplification. As PCR progresses, the DNA generated is itself used as a template for replication,

setting in motion a chain reaction in which the DNA template is exponentially amplified. PCR can be extensively modified to perform a wide array of genetic manipulations.



A strip of eight PCR tubes, each containing a 100 µL reaction mixture

Almost all PCR applications employ a heat-stable DNA polymerase, such as Taq polymerase, an enzyme originally isolated from the bacterium *Thermus aquaticus*. This DNA polymerase enzymatically assembles a new DNA strand from DNA building blocks, the nucleotides, by using single-stranded DNA as a template and DNA oligonucleotides (also called DNA primers), which are required for initiation of DNA synthesis. The vast majority of PCR methods use thermal cycling, i.e., alternately heating and cooling the PCR sample to a defined series of temperature steps. These thermal cycling steps are necessary first to physically separate the two strands in a DNA double helix at a high temperature in a process called DNA melting. At a lower temperature, each strand is then used as the template in DNA synthesis by the DNA polymerase to selectively amplify the target DNA. The selectivity of PCR results from the use of primers that are complementary to the DNA region targeted for amplification under specific thermal cycling conditions.

Developed in 1983 by Kary Mullis,^[1] PCR is now a common and often indispensable technique used in medical and biological research labs for a variety of applications.^{[2] [3]} These include DNA cloning for sequencing, DNA-based phylogeny, or functional analysis of genes; the diagnosis of hereditary diseases; the identification of genetic fingerprints (used in forensic sciences and paternity testing); and the detection and diagnosis of infectious diseases. In 1993, Mullis was awarded the Nobel Prize in Chemistry for his work on PCR.^[4]

PCR principles and procedure

PCR is used to amplify a specific region of a DNA strand (the DNA target). Most PCR methods typically amplify DNA fragments of up to ~10 kilo base pairs (kb), although some techniques allow for amplification of fragments up to 40 kb in size.^[5]

A basic PCR set up requires several components and reagents.^[6] These components include:

- *DNA template* that contains the DNA region (target) to be amplified.
- Two *primers* that are complementary to the 3' (three prime) ends of each of the sense and anti-sense strand of the DNA target.
- *Taq polymerase* or another DNA polymerase with a temperature optimum at around 70 °C.
- *Deoxynucleoside triphosphates* (dNTPs; also very commonly and erroneously called deoxynucleotide triphosphates), the building blocks from which the DNA polymerases synthesizes a new DNA strand.
- *Buffer solution*, providing a suitable chemical environment for optimum activity and stability of the DNA polymerase.
- *Divalent cations*, magnesium or manganese ions; generally Mg^{2+} is used, but Mn^{2+} can be utilized for PCR-mediated DNA mutagenesis, as higher Mn^{2+} concentration increases the error rate during DNA synthesis^[7]
- *Monovalent cation* potassium ions.

The PCR is commonly carried out in a reaction volume of 10–200 μ l in small reaction tubes (0.2–0.5 ml volumes) in a thermal cycler. The thermal cycler heats and cools the reaction tubes to achieve the temperatures required at each step of the reaction (see below). Many modern thermal cyclers make use of the Peltier effect which permits both heating and cooling of the block holding the PCR tubes simply by reversing the electric current. Thin-walled reaction tubes permit favorable thermal conductivity to allow for rapid thermal equilibration. Most thermal cyclers have heated lids to prevent condensation at the top of the reaction tube. Older thermocyclers lacking a heated lid require a layer of oil on top of the reaction mixture or a ball of wax inside the tube.



Figure 1a: A thermal cycler for PCR



Figure 1b: An older model three-temperature thermal cycler for PCR

Procedure

Typically, PCR consists of a series of 20–40 repeated temperature changes, called cycles, with each cycle commonly consisting of 2–3 discrete temperature steps, usually three (Fig. 2). The cycling is often preceded by a single temperature step (called *hold*) at a high temperature ($>90^{\circ}\text{C}$), and followed by one hold at the end for final product extension or brief storage. The temperatures used and the length of time they are applied in each cycle depend on a variety of parameters. These include the enzyme used for DNA synthesis, the concentration of divalent ions and dNTPs in the reaction, and the melting temperature (T_m) of the primers.^[8]

- **Initialization step:** This step consists of heating the reaction to a temperature of $94\text{--}96^{\circ}\text{C}$ (or 98°C if extremely thermostable polymerases are used), which is held for 1–9 minutes. It is only required for DNA polymerases that require heat activation by hot-start PCR.^[9]
- **Denaturation step:** This step is the first regular cycling event and consists of heating the reaction to $94\text{--}98^{\circ}\text{C}$ for 20–30 seconds. It causes DNA melting of the DNA template by disrupting the hydrogen bonds between complementary bases, yielding single-stranded DNA molecules.
- **Annealing step:** The reaction temperature is lowered to $50\text{--}65^{\circ}\text{C}$ for 20–40 seconds allowing annealing of the primers to the single-stranded DNA template. Typically the annealing temperature is about 3–5 degrees Celsius below the T_m of the primers used. Stable DNA–DNA hydrogen bonds are only formed when the primer sequence very closely matches the template sequence. The polymerase binds to the primer–template hybrid and begins DNA synthesis.
- **Extension/elongation step:** The temperature at this step depends on the DNA polymerase used; Taq polymerase has its optimum activity temperature at $75\text{--}80^{\circ}\text{C}$,^{[10] [11]} and commonly a temperature of 72°C is used with this enzyme. At this step the DNA polymerase synthesizes a new DNA strand complementary to the DNA template strand by adding dNTPs that are complementary to the template in 5' to 3' direction, condensing the 5'-phosphate group of the dNTPs with the 3'-hydroxyl group at the end of the nascent (extending) DNA strand. The extension time depends both on the DNA polymerase used and on the length of the DNA fragment to be amplified. As a rule-of-thumb, at its optimum temperature, the DNA polymerase will polymerize a thousand bases per minute. Under optimum conditions, i.e., if there are no limitations due to limiting substrates or reagents, at each extension step, the amount of DNA target is doubled, leading to exponential (geometric) amplification of the specific DNA fragment.
- **Final elongation:** This single step is occasionally performed at a temperature of $70\text{--}74^{\circ}\text{C}$ for 5–15 minutes after the last PCR cycle to ensure that any remaining single-stranded DNA is fully extended.
- **Final hold:** This step at $4\text{--}15^{\circ}\text{C}$ for an indefinite time may be employed for short-term storage of the reaction.

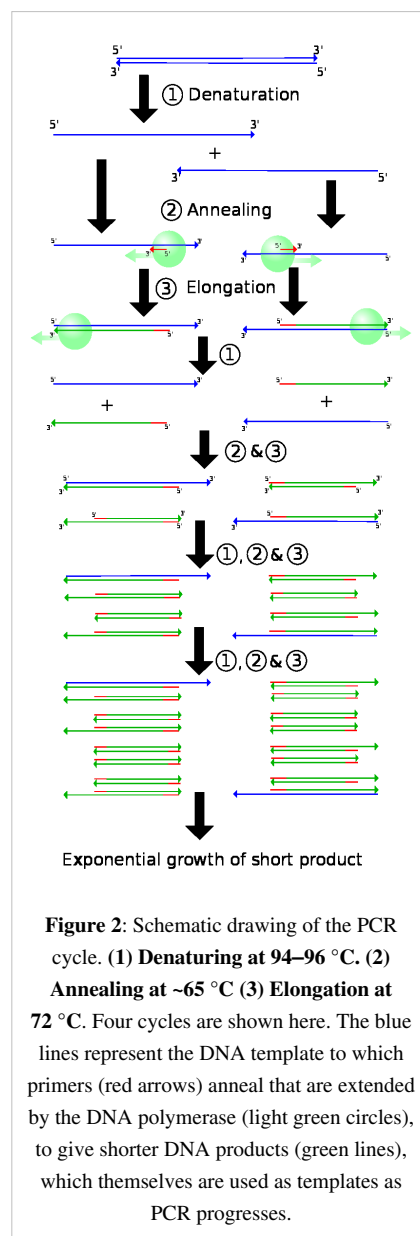


Figure 2: Schematic drawing of the PCR cycle. (1) **Denaturing at $94\text{--}96^{\circ}\text{C}$.** (2) **Annealing at $\sim 65^{\circ}\text{C}$** (3) **Elongation at 72°C .** Four cycles are shown here. The blue lines represent the DNA template to which primers (red arrows) anneal that are extended by the DNA polymerase (light green circles), to give shorter DNA products (green lines), which themselves are used as templates as PCR progresses.

To check whether the PCR generated the anticipated DNA fragment (also sometimes referred to as the amplicon or amplicon), agarose gel electrophoresis is employed for size separation of the PCR products. The size(s) of PCR products is determined by comparison with a DNA ladder (a molecular weight marker), which contains DNA fragments of known size, run on the gel alongside the PCR products (see Fig. 3).

PCR stages

The PCR process can be divided into three stages:

Exponential amplification: At every cycle, the amount of product is doubled (assuming 100% reaction efficiency). The reaction is very sensitive: only minute quantities of DNA need to be present.^[12]

Levelling off stage: The reaction slows as the DNA polymerase loses activity and as consumption of reagents such as dNTPs and primers causes them to become limiting.

Plateau: No more product accumulates due to exhaustion of reagents and enzyme.

PCR optimization

In practice, PCR can fail for various reasons, in part due to its sensitivity to contamination causing amplification of spurious DNA products. Because of this, a number of techniques and procedures have been developed for optimizing PCR conditions.^{[13] [14]} Contamination with extraneous DNA is addressed with lab protocols and procedures that separate pre-PCR mixtures from potential DNA contaminants.^[6] This usually involves spatial separation of PCR-setup areas from areas for analysis or purification of PCR products, use of disposable plasticware, and thoroughly cleaning the work surface between reaction setups. Primer-design techniques are important in improving PCR product yield and in avoiding the formation of spurious products, and the usage of alternate buffer components or polymerase enzymes can help with amplification of long or otherwise problematic regions of DNA.

Application of PCR

Selective DNA isolation

PCR allows isolation of DNA fragments from genomic DNA by selective amplification of a specific region of DNA. This use of PCR augments many methods, such as generating hybridization probes for Southern or northern hybridization and DNA cloning, which require larger amounts of DNA, representing a specific DNA region. PCR supplies these techniques with high amounts of pure DNA, enabling analysis of DNA samples even from very small amounts of starting material.

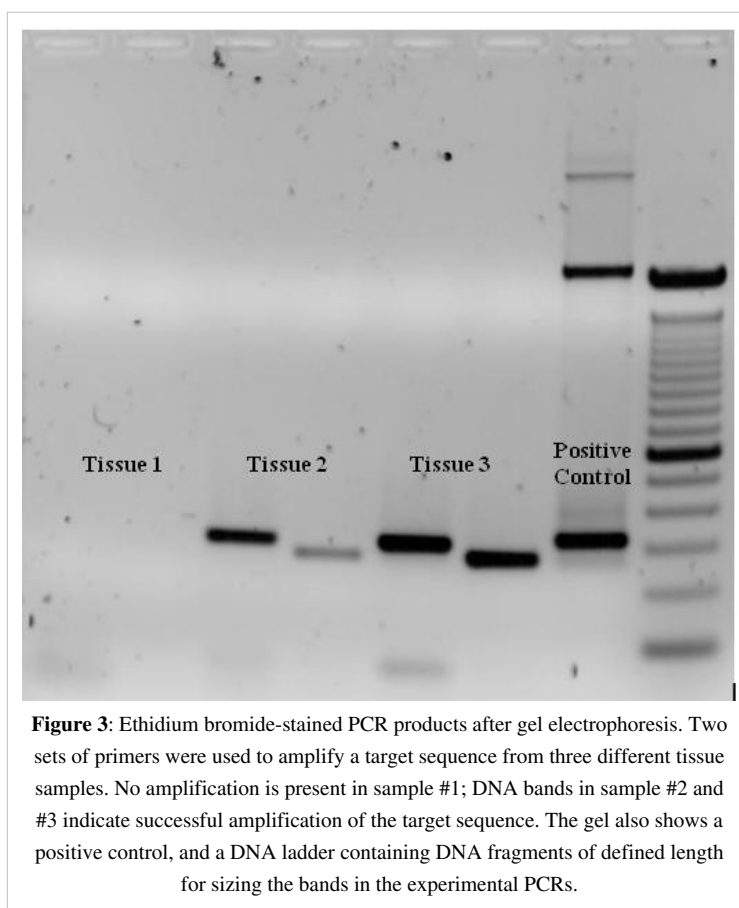


Figure 3: Ethidium bromide-stained PCR products after gel electrophoresis. Two sets of primers were used to amplify a target sequence from three different tissue samples. No amplification is present in sample #1; DNA bands in sample #2 and #3 indicate successful amplification of the target sequence. The gel also shows a positive control, and a DNA ladder containing DNA fragments of defined length for sizing the bands in the experimental PCRs.

Other applications of PCR include DNA sequencing to determine unknown PCR-amplified sequences in which one of the amplification primers may be used in Sanger sequencing, isolation of a DNA sequence to expedite recombinant DNA technologies involving the insertion of a DNA sequence into a plasmid or the genetic material of another organism. Bacterial colonies (*E. coli*) can be rapidly screened by PCR for correct DNA vector constructs.^[15] PCR may also be used for genetic fingerprinting; a forensic technique used to identify a person or organism by comparing experimental DNAs through different PCR-based methods.

Some PCR 'fingerprints' methods have high discriminative power and can be used to identify genetic relationships between individuals, such as parent-child or between siblings, and are used in paternity testing (Fig. 4). This technique may also be used to determine evolutionary relationships among organisms.

Amplification and quantification of DNA

Because PCR amplifies the regions of DNA that it targets, PCR can be used to analyze extremely small amounts of sample. This is often critical for forensic analysis, when only a trace amount of DNA is available as evidence. PCR may also be used in the analysis of ancient DNA that is tens of thousands of years old. These PCR-based techniques have been successfully used on animals, such as a forty-thousand-year-old mammoth, and also on human DNA, in applications ranging from the analysis of Egyptian mummies to the identification of a Russian tsar.^[16]

Quantitative PCR methods allow the estimation of the amount of a given sequence present in a sample—a technique often applied to quantitatively determine levels of gene expression. Real-time PCR is an established tool for DNA quantification that measures the accumulation of DNA product after each round of PCR amplification.

- See also Use of DNA in forensic entomology

PCR in diagnosis of diseases

PCR permits early diagnosis of malignant diseases such as leukemia and lymphomas, which is currently the highest developed in cancer research and is already being used routinely. PCR assays can be performed directly on genomic DNA samples to detect translocation-specific malignant cells at a sensitivity which is at least 10,000 fold higher than other methods.

PCR also permits identification of non-cultivable or slow-growing microorganisms such as mycobacteria, anaerobic bacteria, or viruses from tissue culture assays and animal models. The basis for PCR diagnostic applications in microbiology is the detection of infectious agents and the discrimination of non-pathogenic from pathogenic strains by virtue of specific genes.

Viral DNA can likewise be detected by PCR. The primers used need to be specific to the targeted sequences in the DNA of a virus, and the PCR can be used for diagnostic analyses or DNA sequencing of the viral genome. The high sensitivity of PCR permits virus detection soon after infection and even before the onset of disease. Such early detection may give physicians a significant lead in treatment. The amount of virus ("viral load") in a patient can also be quantified by PCR-based DNA quantitation techniques (see below).

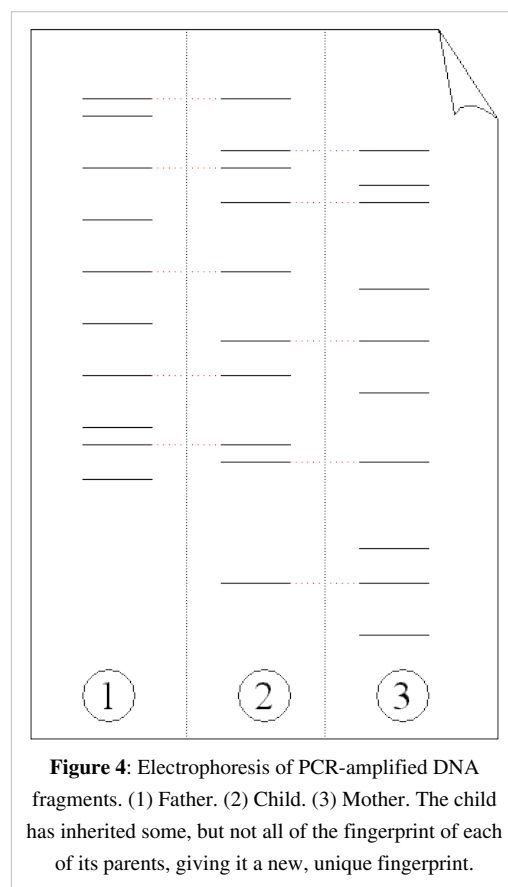


Figure 4: Electrophoresis of PCR-amplified DNA fragments. (1) Father. (2) Child. (3) Mother. The child has inherited some, but not all of the fingerprint of each of its parents, giving it a new, unique fingerprint.

Variations on the basic PCR technique

- *Allele-specific PCR*: a diagnostic or cloning technique which is based on single-nucleotide polymorphisms (SNPs) (single-base differences in DNA). It requires prior knowledge of a DNA sequence, including differences between alleles, and uses primers whose 3' ends encompass the SNP. PCR amplification under stringent conditions is much less efficient in the presence of a mismatch between template and primer, so successful amplification with an SNP-specific primer signals presence of the specific SNP in a sequence.^[17] See SNP genotyping for more information.
 - *Assembly PCR* or *Polymerase Cycling Assembly (PCA)*: artificial synthesis of long DNA sequences by performing PCR on a pool of long oligonucleotides with short overlapping segments. The oligonucleotides alternate between sense and antisense directions, and the overlapping segments determine the order of the PCR fragments, thereby selectively producing the final long DNA product.^[18]
 - *Asymmetric PCR*: preferentially amplifies one DNA strand in a double-stranded DNA template. It is used in sequencing and hybridization probing where amplification of only one of the two complementary strands is required. PCR is carried out as usual, but with a great excess of the primer for the strand targeted for amplification. Because of the slow (arithmetic) amplification later in the reaction after the limiting primer has been used up, extra cycles of PCR are required.^[19] A recent modification on this process, known as *Linear-After-The-Exponential-PCR (LATE-PCR)*, uses a limiting primer with a higher melting temperature (T_m) than the excess primer to maintain reaction efficiency as the limiting primer concentration decreases mid-reaction.^[20]
 - *Helicase-dependent amplification*: similar to traditional PCR, but uses a constant temperature rather than cycling through denaturation and annealing/extension cycles. DNA helicase, an enzyme that unwinds DNA, is used in place of thermal denaturation.^[21]
 - *Hot-start PCR*: a technique that reduces non-specific amplification during the initial set up stages of the PCR. It may be performed manually by heating the reaction components to the melting temperature (e.g., 95°C) before adding the polymerase.^[22] Specialized enzyme systems have been developed that inhibit the polymerase's activity at ambient temperature, either by the binding of an antibody^[9] ^[23] or by the presence of covalently bound inhibitors that only dissociate after a high-temperature activation step. Hot-start/cold-finish PCR is achieved with new hybrid polymerases that are inactive at ambient temperature and are instantly activated at elongation temperature.
 - *Intersequence-specific PCR (ISSR)*: a PCR method for DNA fingerprinting that amplifies regions between simple sequence repeats to produce a unique fingerprint of amplified fragment lengths.^[24]
 - *Inverse PCR*: is commonly used to identify the flanking sequences around genomic inserts. It involves a series of DNA digestions and self ligation, resulting in known sequences at either end of the unknown sequence.^[25]
 - *Ligation-mediated PCR*: uses small DNA linkers ligated to the DNA of interest and multiple primers annealing to the DNA linkers; it has been used for DNA sequencing, genome walking, and DNA footprinting.^[26]
 - *Methylation-specific PCR (MSP)*: developed by Stephen Baylin and Jim Herman at the Johns Hopkins School of Medicine,^[27] and is used to detect methylation of CpG islands in genomic DNA. DNA is first treated with sodium bisulfite, which converts unmethylated cytosine bases to uracil, which is recognized by PCR primers as thymine. Two PCRs are then carried out on the modified DNA, using primer sets identical except at any CpG islands within the primer sequences. At these points, one primer set recognizes DNA with cytosines to amplify methylated DNA, and one set recognizes DNA with uracil or thymine to amplify unmethylated DNA. MSP using qPCR can also be performed to obtain quantitative rather than qualitative information about methylation.
 - *Miniprimer PCR*: uses a thermostable polymerase (S-Tbr) that can extend from short primers ("smalligos") as short as 9 or 10 nucleotides. This method permits PCR targeting to smaller primer binding regions, and is used to amplify conserved DNA sequences, such as the 16S (or eukaryotic 18S) rRNA gene.^[28]
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- *Multiplex Ligation-dependent Probe Amplification (MLPA)*: permits multiple targets to be amplified with only a single primer pair, thus avoiding the resolution limitations of multiplex PCR (see below).
- *Multiplex-PCR*: consists of multiple primer sets within a single PCR mixture to produce amplicons of varying sizes that are specific to different DNA sequences. By targeting multiple genes at once, additional information may be gained from a single test run that otherwise would require several times the reagents and more time to perform. Annealing temperatures for each of the primer sets must be optimized to work correctly within a single reaction, and amplicon sizes, i.e., their base pair length, should be different enough to form distinct bands when visualized by gel electrophoresis.
- *Nested PCR*: increases the specificity of DNA amplification, by reducing background due to non-specific amplification of DNA. Two sets of primers are used in two successive PCRs. In the first reaction, one pair of primers is used to generate DNA products, which besides the intended target, may still consist of non-specifically amplified DNA fragments. The product(s) are then used in a second PCR with a set of primers whose binding sites are completely or partially different from and located 3' of each of the primers used in the first reaction. Nested PCR is often more successful in specifically amplifying long DNA fragments than conventional PCR, but it requires more detailed knowledge of the target sequences.
- *Overlap-extension PCR*: a genetic engineering technique allowing the construction of a DNA sequence with an alteration inserted beyond the limit of the longest practical primer length.
- *Quantitative PCR (Q-PCR)*: used to measure the quantity of a PCR product (commonly in real-time). It quantitatively measures starting amounts of DNA, cDNA or RNA. Q-PCR is commonly used to determine whether a DNA sequence is present in a sample and the number of its copies in the sample. *Quantitative real-time PCR* has a very high degree of precision. QRT-PCR methods use fluorescent dyes, such as Sybr Green, EvaGreen or fluorophore-containing DNA probes, such as TaqMan, to measure the amount of amplified product in real time. It is also sometimes abbreviated to RT-PCR (Real Time PCR) or RQ-PCR. QRT-PCR or RTQ-PCR are more appropriate contractions, since RT-PCR commonly refers to reverse transcription PCR (see below), often used in conjunction with Q-PCR.
- *Reverse Transcription PCR (RT-PCR)*: for amplifying DNA from RNA. Reverse transcriptase reverse transcribes RNA into cDNA, which is then amplified by PCR. RT-PCR is widely used in expression profiling, to determine the expression of a gene or to identify the sequence of an RNA transcript, including transcription start and termination sites. If the genomic DNA sequence of a gene is known, RT-PCR can be used to map the location of exons and introns in the gene. The 5' end of a gene (corresponding to the transcription start site) is typically identified by RACE-PCR (*Rapid Amplification of cDNA Ends*).
- *Solid Phase PCR*: encompasses multiple meanings, including Polony Amplification (where PCR colonies are derived in a gel matrix, for example), Bridge PCR^[29] (primers are covalently linked to a solid-support surface), conventional Solid Phase PCR (where Asymmetric PCR is applied in the presence of solid support bearing primer with sequence matching one of the aqueous primers) and Enhanced Solid Phase PCR^[30] (where conventional Solid Phase PCR can be improved by employing high T_m and nested solid support primer with optional application of a thermal 'step' to favour solid support priming).
- *Thermal asymmetric interlaced PCR (TAIL-PCR)*: for isolation of an unknown sequence flanking a known sequence. Within the known sequence, TAIL-PCR uses a nested pair of primers with differing annealing temperatures; a degenerate primer is used to amplify in the other direction from the unknown sequence.^[31]
- *Touchdown PCR (Step-down PCR)*: a variant of PCR that aims to reduce nonspecific background by gradually lowering the annealing temperature as PCR cycling progresses. The annealing temperature at the initial cycles is usually a few degrees (3-5°C) above the T_m of the primers used, while at the later cycles, it is a few degrees (3-5°C) below the primer T_m . The higher temperatures give greater specificity for primer binding, and the lower temperatures permit more efficient amplification from the specific products formed during the initial cycles.^[32]

- *PAN-AC*: uses isothermal conditions for amplification, and may be used in living cells.^{[33] [34]}
- *Universal Fast Walking*: for genome walking and genetic fingerprinting using a more specific 'two-sided' PCR than conventional 'one-sided' approaches (using only one gene-specific primer and one general primer - which can lead to artefactual 'noise')^[35] by virtue of a mechanism involving lariat structure formation. Streamlined derivatives of UFW are LaNe RAGE (lariat-dependent nested PCR for rapid amplification of genomic DNA ends),^[36] 5'RACE LaNe^[37] and 3'RACE LaNe.^[38]

History

A 1971 paper in the *Journal of Molecular Biology* by Kleppe and co-workers first described a method using an enzymatic assay to replicate a short DNA template with primers *in vitro*.^[39] However, this early manifestation of the basic PCR principle did not receive much attention, and the invention of the polymerase chain reaction in 1983 is generally credited to Kary Mullis.^[40]

At the core of the PCR method is the use of a suitable DNA polymerase able to withstand the high temperatures of >90 °C (194 °F) required for separation of the two DNA strands in the DNA double helix after each replication cycle. The DNA polymerases initially employed for *in vitro* experiments presaging PCR were unable to withstand these high temperatures.^[2] So the early procedures for DNA replication were very inefficient, time consuming, and required large amounts of DNA polymerase and continual handling throughout the process.

The discovery in 1976 of Taq polymerase — a DNA polymerase purified from the thermophilic bacterium, *Thermus aquaticus*, which naturally lives in hot (50 to 80 °C (122 to 176 °F)) environments^[10] such as hot springs — paved the way for dramatic improvements of the PCR method. The DNA polymerase isolated from *T. aquaticus* is stable at high temperatures remaining active even after DNA denaturation,^[11] thus obviating the need to add new DNA polymerase after each cycle.^[3] This allowed an automated thermocycler-based process for DNA amplification.

When Mullis developed the PCR in 1983, he was working in Emeryville, California for Cetus Corporation, one of the first biotechnology companies. There, he was responsible for synthesizing short chains of DNA. Mullis has written that he conceived of PCR while cruising along the Pacific Coast Highway one night in his car.^[41] He was playing in his mind with a new way of analyzing changes (mutations) in DNA when he realized that he had instead invented a method of amplifying any DNA region through repeated cycles of duplication driven by DNA polymerase. In *Scientific American*, Mullis summarized the procedure: "Beginning with a single molecule of the genetic material DNA, the PCR can generate 100 billion similar molecules in an afternoon. The reaction is easy to execute. It requires no more than a test tube, a few simple reagents, and a source of heat."^[42] He was awarded the Nobel Prize in Chemistry in 1993 for his invention,^[4] seven years after he and his colleagues at Cetus first put his proposal to practice. However, some controversies have remained about the intellectual and practical contributions of other scientists to Mullis' work, and whether he had been the sole inventor of the PCR principle (see below).

Patent wars

The PCR technique was patented by Kary Mullis and assigned to Cetus Corporation, where Mullis worked when he invented the technique in 1983. The *Taq* polymerase enzyme was also covered by patents. There have been several high-profile lawsuits related to the technique, including an unsuccessful lawsuit brought by DuPont. The pharmaceutical company Hoffmann-La Roche purchased the rights to the patents in 1992 and currently holds those that are still protected.

A related patent battle over the Taq polymerase enzyme is still ongoing in several jurisdictions around the world between Roche and Promega. The legal arguments have extended beyond the lives of the original PCR and Taq polymerase patents, which expired on March 28, 2005.^[43]

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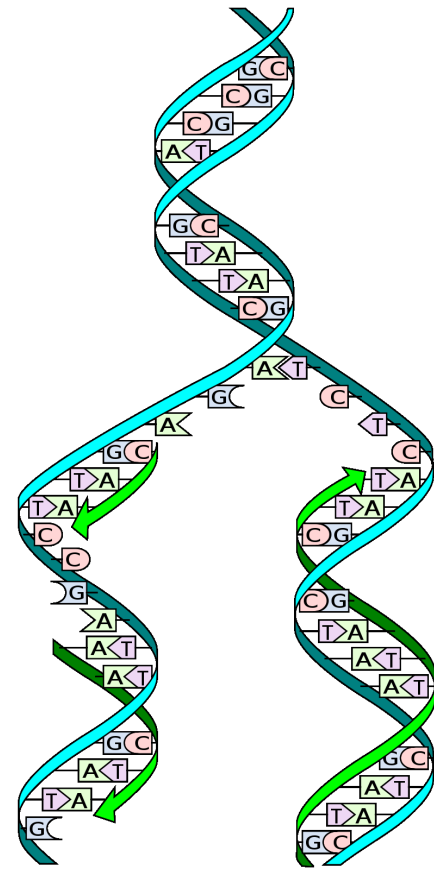
- US Patent for PCR (<http://patft.uspto.gov/netacgi/nph-Parser?Sect2=PTO1&Sect2=HITOFF&p=1&u=/netahtml/PTO/search-bool.html&r=1&f=G&l=50&d=PALL&RefSrch=yes&Query=PN/4683202>)
- Step-through animation of PCR (<http://www.dnalc.org/ddnalc/resources/pcr.html>) - Cold Spring Harbor Laboratory
- OpenWetWare (<http://openwetware.org/wiki/PCR>)
- OpenPCR (<http://openpcr.org>)

DNA replication

DNA replication, the basis for biological inheritance, is a fundamental process that occurs in all living organisms that copies their DNA. This process is "replication" in that each strand of the original double-stranded DNA molecule serves as template for the reproduction of the complementary strand. Therefore, following DNA replication, two identical DNA molecules have been produced from a single double-stranded DNA molecule. Cellular proofreading and error toe-checking mechanisms ensure near perfect fidelity for DNA replication.^{[1] [2]}

In a cell, DNA replication begins at specific locations in the genome, called "origins".^[3] Unwinding of DNA at the origin, and synthesis of new strands, forms a replication fork. In addition to DNA polymerase, the enzyme that synthesizes the new DNA by adding nucleotides matched to the template strand, a number of other proteins are associated with the fork and assist in the initiation and continuation of DNA synthesis.

DNA replication can also be performed *in vitro* (outside a cell). DNA polymerases, isolated from cells, and artificial DNA primers are used to initiate DNA synthesis at known sequences in a template molecule. The polymerase chain reaction (PCR), a common laboratory technique, employs such artificial synthesis in a cyclic manner to amplify a specific target DNA fragment from a pool of DNA.



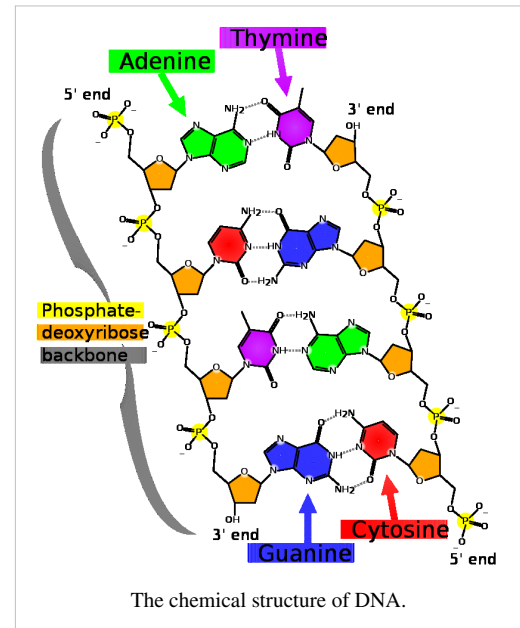
DNA replication. The double helix is unwound and each strand acts as a template. Bases are matched to synthesize the new partner strands.

DNA structure

DNA usually exists as a double-stranded structure, with both strands coiled together to form the characteristic double-helix. Each single strand of DNA is a chain of four types of nucleotides: adenine, cytosine, guanine, and thymine. A nucleotide is a mono-, di- or triphosphate deoxyribonucleoside; that is, a deoxyribose sugar is attached to one, two or three phosphates. Chemical interaction of these nucleotides forms phosphodiester linkages, creating the phosphate-deoxyribose backbone of the DNA double helix with the bases pointing inward. Nucleotides (bases) are matched between strands through hydrogen bonds to form base pairs. Adenine pairs with thymine and cytosine pairs with guanine.

DNA strands have a directionality, and the different ends of a single strand are called the "3' (three-prime) end" and the "5' (five-prime) end." These terms refer to the carbon atom in deoxyribose to which the next phosphate in the chain attaches. In addition to being complementary, the two strands of DNA are antiparallel: they are orientated in opposite directions. This directionality has consequences in DNA synthesis, because DNA polymerase can only synthesize DNA in one direction by adding nucleotides to the 3' end of a DNA strand.

The pairing of bases in DNA through hydrogen bonding means that the information contained within each strand is redundant. The nucleotides on a single strand can be used to reconstruct nucleotides on a newly synthesized partner strand.^[4]

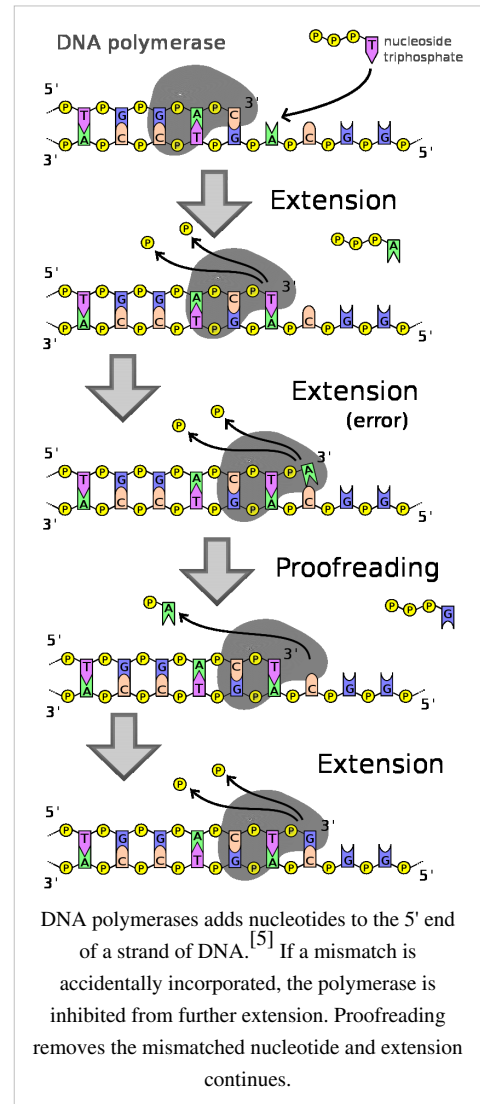


DNA polymerase

DNA polymerases are a family of enzymes that carry out all forms of DNA replication.^[6] A DNA polymerase can only extend an existing DNA strand paired with a template strand; it cannot begin the synthesis of a new strand. To begin synthesis of a new strand, a short fragment of DNA or RNA, called a primer, must be created and paired with the template strand before DNA polymerase can synthesize new DNA.

Once a primer pairs with DNA to be replicated, DNA polymerase synthesizes a new strand of DNA by extending the 3' end of an existing nucleotide chain, adding new nucleotides matched to the template strand one at a time via the creation of phosphodiester bonds. The energy for this process of DNA polymerization comes from two of the three total phosphates attached to each unincorporated base. (Free bases with their attached phosphate groups are called nucleoside triphosphates.) When a nucleotide is being added to a growing DNA strand, two of the phosphates are removed and the energy produced creates a phosphodiester (chemical) bond that attaches the remaining phosphate to the growing chain. The energetics of this process also help explain the directionality of synthesis - if DNA were synthesized in the 3' to 5' direction, the energy for the process would come from the 5' end of the growing strand rather than from free nucleotides.

DNA polymerases are generally extremely accurate, making less than one error for every 10^7 nucleotides added.^[7] Even so, some DNA polymerases also have proofreading ability; they can remove nucleotides from the end of a strand in order to correct mismatched bases. If the 5' nucleotide needs to be removed during proofreading, the triphosphate end is lost. Hence, the energy source that usually provides energy to add a new nucleotide is also lost.



DNA replication within the cell

Origins of replication

For a cell to divide, it must first replicate its DNA.^[8] This process is initiated at particular points within the DNA, known as "origins", which are targeted by proteins that separate the two strands and initiate DNA synthesis.^[3] Origins contain DNA sequences recognized by replication initiator proteins (e.g. *dnaA* in *E. coli* and the Origin Recognition Complex in yeast).^[9] These initiator proteins recruit other proteins to separate the two strands and initiate replication forks.

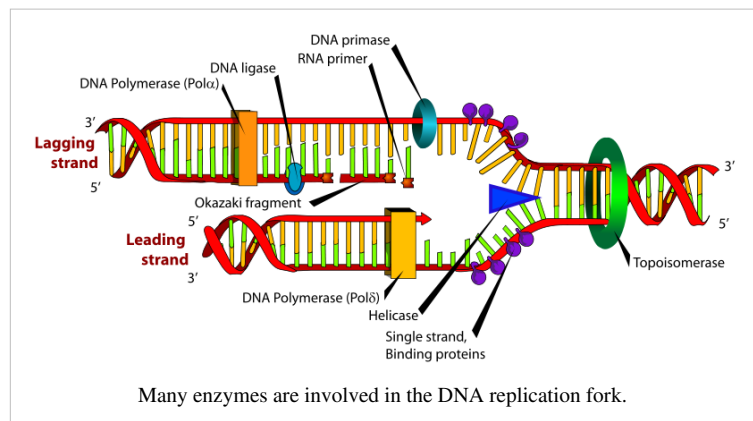
Initiator proteins recruit other proteins to separate the DNA strands at the origin, forming a bubble. Origins tend to be "AT-rich" (rich in adenine and thymine bases) to assist this process, because A-T base pairs have two hydrogen bonds (rather than the three formed in a C-G pair)—strands rich in these nucleotides are generally easier to separate due to the positive relationship between the number of hydrogen bonds and the difficulty of breaking these bonds.^[10] Once strands are separated, RNA primers are created on the template strands. More specifically, the leading strand receives one RNA primer per active origin of replication while the lagging strand receives several; these several fragments of RNA primers found on the lagging strand of DNA are called Okazaki fragments, named after their

discoverer. DNA Polymerase extends the leading strand in one continuous motion and the lagging strand in a discontinuous motion (due to the Okazaki fragments). RNase removes the RNA fragments used to initiate replication by DNA Polymerase, and another DNA Polymerase enters to fill the gaps. When this is complete, a single nick on the leading strand and several nicks on the lagging strand can be found. Ligase works to fill these nicks in, thus completing the newly replicated DNA molecule.

As DNA synthesis continues, the original DNA strands continue to unwind on each side of the bubble, forming 2 replication forks. In bacteria, which have a single origin of replication on their circular chromosome, this process eventually creates a "theta structure" (resembling the Greek letter theta: θ). In contrast, eukaryotes have longer linear chromosomes and initiate replication at multiple origins within these.

The replication fork

The replication fork is a structure that forms within the nucleus during DNA replication. It is created by helicases, which break the hydrogen bonds holding the two DNA strands together. The resulting structure has two branching "prongs", each one made up of a single strand of DNA. These two strands serve as the template for the leading and lagging strands which will be created as DNA polymerase matches complementary nucleotides to the templates; The templates may be properly referred to as the leading strand template and the lagging strand template.



Leading strand

The leading strand is the template strand of the DNA double helix so that the replication fork moves along it in the 3' to 5' direction. This allows the new strand synthesized complementary to it to be synthesized 5' to 3' in the same direction as the movement of the replication fork.

On the leading strand, a polymerase "reads" the DNA and adds nucleotides to it continuously. This polymerase is DNA polymerase III (DNA Pol III) in prokaryotes and presumably Pol ϵ ^[11] [12] in eukaryotes.

Lagging strand

The lagging strand is the strand of the template DNA double helix that is oriented so that the replication fork moves along it in a 5' to 3' manner. Because of its orientation, opposite to the working orientation of DNA polymerase III, which moves on a template in a 3' to 5' manner, replication of the lagging strand is more complicated than that of the leading strand.

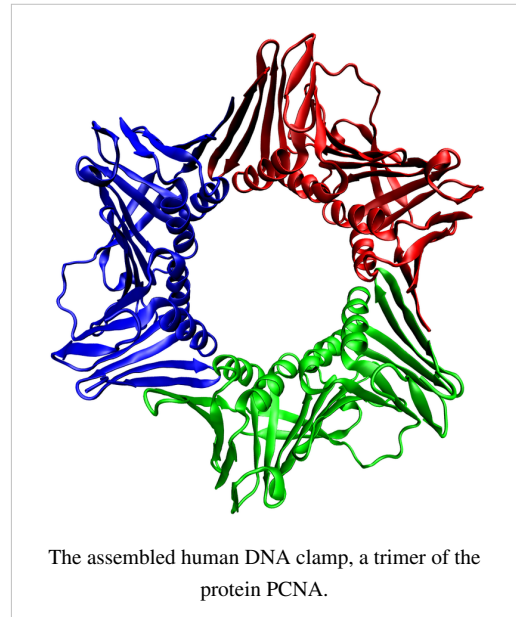
On the lagging strand, primase "reads" the DNA and adds RNA to it in short, separated segments. In eukaryotes, primase is intrinsic to Pol α .^[13] DNA polymerase III or Pol δ lengthens the primed segments, forming Okazaki fragments. Primer removal in eukaryotes is also performed by Pol δ .^[14] In prokaryotes, DNA polymerase I "reads" the fragments, removes the RNA using its flap endonuclease domain (RNA primers are removed by 5'-3' exonuclease activity of polymerase I [weaver, 2005], and replaces the RNA nucleotides with DNA nucleotides (this is necessary because RNA and DNA use slightly different kinds of nucleotides). DNA ligase joins the fragments together.

Dynamics at the replication fork

As helicase unwinds DNA at the replication fork, the DNA ahead is forced to rotate. This process results in a build-up of twists in the DNA ahead.^[15] This build-up would form a resistance that would eventually halt the progress of the replication fork. DNA topoisomerases are enzymes that solve these physical problems in the coiling of DNA. Topoisomerase I cuts a single backbone on the DNA, enabling the strands to swivel around each other to remove the build-up of twists. Topoisomerase II cuts both backbones, enabling one double-stranded DNA to pass through another, thereby removing knots and entanglements that can form within and between DNA molecules.

Bare single-stranded DNA has a tendency to fold back upon itself and form secondary structures; these structures can interfere with the movement of DNA polymerase. To prevent this, single-strand binding proteins bind to the DNA until a second strand is synthesized, preventing secondary structure formation.^[16]

Clamp proteins form a sliding clamp around DNA, helping the DNA polymerase maintain contact with its template and thereby assisting with processivity. The inner face of the clamp enables DNA to be threaded through it. Once the polymerase reaches the end of the template or detects double stranded DNA, the sliding clamp undergoes a conformational change which releases the DNA polymerase. Clamp-loading proteins are used to initially load the clamp, recognizing the junction between template and RNA primers.



Regulation of replication

Eukaryotes

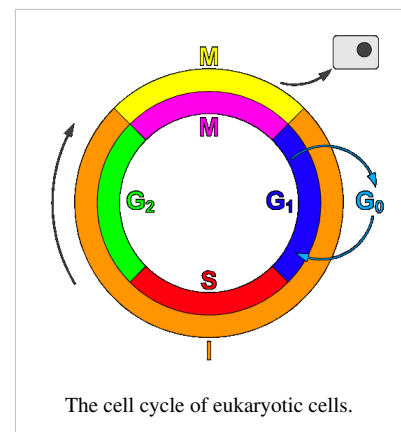
Within eukaryotes, DNA replication is controlled within the context of the cell cycle. As the cell grows and divides, it progresses through stages in the cell cycle; DNA replication occurs during the S phase (Synthesis phase). The progress of the eukaryotic cell through the cycle is controlled by cell cycle checkpoints. Progression through checkpoints is controlled through complex interactions between various proteins, including cyclins and cyclin-dependent kinases.^[17]

The G1/S checkpoint (or restriction checkpoint) regulates whether eukaryotic cells enter the process of DNA replication and subsequent division. Cells which do not proceed through this checkpoint are quiescent in the "G0" stage and do not replicate their DNA.

Replication of chloroplast and mitochondrial genomes occurs independent of the cell cycle, through the process of D-loop replication.

Bacteria

Most bacteria do not go through a well-defined cell cycle and instead continuously copy their DNA; during rapid growth this can result in multiple rounds of replication occurring concurrently.^[18] Within *E. coli*, the most well-characterized bacteria, regulation of DNA replication can be achieved through several mechanisms, including: the hemimethylation and sequestering of the origin sequence, the ratio of ATP to ADP, and the levels of protein DnaA. These all control the process of initiator proteins binding to the origin sequences.



Because *E. coli* methylates GATC DNA sequences, DNA synthesis results in hemimethylated sequences. This hemimethylated DNA is recognized by a protein (SeqA) which binds and sequesters the origin sequence; in addition, dnaA (required for initiation of replication) binds less well to hemimethylated DNA. As a result, newly replicated origins are prevented from immediately initiating another round of DNA replication.^[19]

ATP builds up when the cell is in a rich medium, triggering DNA replication once the cell has reached a specific size. ATP competes with ADP to bind to DnaA, and the DnaA-ATP complex is able to initiate replication. A certain number of DnaA proteins are also required for DNA replication — each time the origin is copied the number of binding sites for DnaA doubles, requiring the synthesis of more DnaA to enable another initiation of replication.

Termination of replication

Because bacteria have circular chromosomes, termination of replication occurs when the two replication forks meet each other on the opposite end of the parental chromosome. *E. coli* regulate this process through the use of termination sequences which, when bound by the Tus protein, enable only one direction of replication fork to pass through. As a result, the replication forks are constrained to always meet within the termination region of the chromosome.^[20]

Eukaryotes initiate DNA replication at multiple points in the chromosome, so replication forks meet and terminate at many points in the chromosome; these are not known to be regulated in any particular manner. Because eukaryotes have linear chromosomes, DNA replication often fails to synthesize to the very end of the chromosomes (telomeres), resulting in telomere shortening. This is a normal process in somatic cells — cells are only able to divide a certain number of times before the DNA loss prevents further division. (This is known as the Hayflick limit.) Within the germ cell line, which passes DNA to the next generation, telomerase extends the repetitive sequences of the telomere region to prevent degradation. Telomerase can become mistakenly active in somatic cells, sometimes leading to cancer formation.

Polymerase chain reaction

Researchers commonly replicate DNA *in vitro* using the polymerase chain reaction (PCR). PCR uses a pair of primers to span a target region in template DNA, and then polymerizes partner strands in each direction from these primers using a thermostable DNA polymerase. Repeating this process through multiple cycles produces amplification of the targeted DNA region. At the start of each cycle, the mixture of template and primers is heated, separating the newly synthesized molecule and template. Then, as the mixture cools, both of these become templates for annealing of new primers, and the polymerase extends from these. As a result, the number of copies of the target region doubles each round, increasing exponentially.^[21]

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The Double Helix

The Double Helix: A Personal Account of the Discovery of the Structure of DNA is an autobiographical account of the discovery of the double helix structure of DNA written by James D. Watson and published in 1968. It was and remains a controversial account. Though it was originally slated to be published by Harvard University Press, Watson's home university dropped the arrangement after protestations from Francis Crick and Maurice Wilkins,^[1] co-discoverers of the structure of DNA, and it was published privately. It has been criticized as being excessively sexist towards Rosalind Franklin, another participant in the discovery, who was deceased by the time Watson's book was written. In 1998, the Modern Library placed *The Double Helix* at number 7 on its list of the 20th century's best works of non-fiction.

The intimate first-person account of scientific discovery was unusual for its time. The book has been hailed as a highly personal view of scientific work, with its author seemingly caring only about the glory of priority and willing to appropriate data from others surreptitiously in order to obtain it. A 1980 Norton Critical Edition of *The Double Helix* edited by Gunther Stent, analyzed the events surrounding its initial publication. It presents a selection of both positive and negative reviews of the book, by such figures as Philip Morrison, Richard Lewontin, Alex Comfort, Jacob Bronowski, and more in-depth analyses by Peter Medawar, Robert K. Merton, and Andre Lwoff. Erwin Chargaff declined permission to reprint his unsympathetic review from the March 29, 1968 issue of *Science*, but letters in response from Max Perutz, Maurice Wilkins, and Watson are printed. Also included are retrospectives from a 1974 edition of *Nature* written by Francis Crick and Linus Pauling, and an analysis of Franklin's work by her student Aaron Klug. The Norton edition concludes with the 1953 papers on DNA structure as published in *Nature*.

The book was made into a film dramatization as *The Race for the Double Helix* in 1987.

Other criticism

The book leaned heavily on personalities, and some, like Rosalind Franklin, were treated cartoonishly.

Burton Feldman^[1]

In the book *Rosalind Franklin and DNA*, author Anne Sayre is very critical of Watson's account. She claims that Watson's book did not give a balanced description of Rosalind Franklin and the nature of her interactions with Maurice Wilkins at King's College, London. Sayre's book raises doubts about the ethics of how Watson and Crick used some of Franklin's results and whether adequate credit was given to her. Watson had very limited contact with Franklin during the time she worked on DNA. By providing more information about Franklin's life than was included in Watson's book, it was possible for Sayre to provide a different perspective on the role Franklin played in Watson and Crick's discovery of the double helix structure of DNA. (See: King's College (London) DNA Controversy)

In the book's preface, Watson explains that he is describing his impressions at the time of the events, and not at the time he wrote the book. In the epilogue Watson writes; *Since my initial impressions about [Franklin], both scientific and personal (as recorded in the early pages of this book) were often wrong I want to say something here about her achievements.* He goes on to describe her superb work, and, despite this, the enormous barriers she faced as a woman in the field of science. He also acknowledged that it took years to overcome their bickering before appreciating Franklin's generosity and integrity.

Notes

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External links

- Photos of the first edition of The Double Helix (<http://www.mansionbooks.com/BookDetail.php?bk=206>)

Nucleic acid double helix

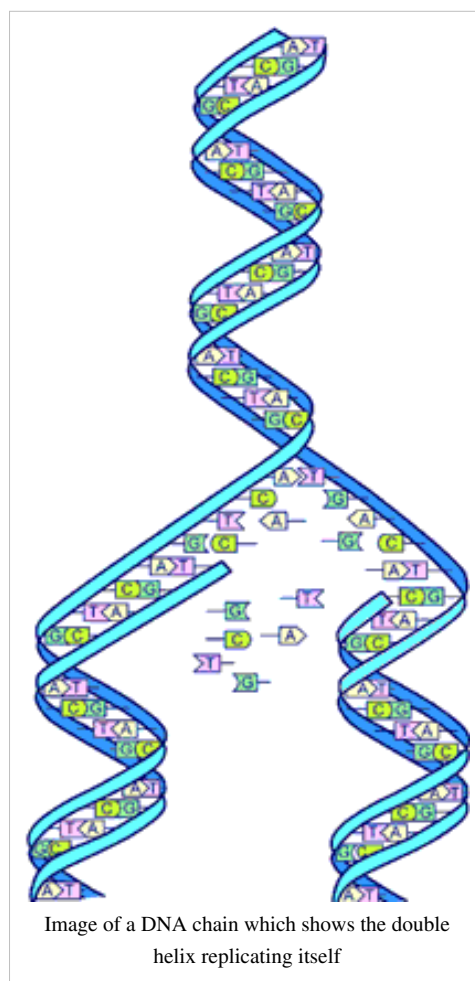
In molecular biology, the term **double helix**^[1] refers to the structure formed by double-stranded molecules of nucleic acids such as DNA and RNA. The double helical structure of a nucleic acid complex arises as a consequence of its secondary structure, and is a fundamental component in determining its tertiary structure. The term entered popular culture with the publication in 1968 of *The Double Helix: A Personal Account of the Discovery of the Structure of DNA*, by James Watson.

The DNA double helix is a spiral polymer of nucleic acids, held together by nucleotides which base pair together.^[2] In B-DNA, the most common double helical structure, the double helix is right-handed with about 10–10.5 nucleotides per turn.^[3] The double helix structure of DNA contains a **major groove** and **minor groove**, the major groove being wider than the minor groove.^[2] Given the difference in widths of the major groove and minor groove, many proteins which bind to DNA do so through the wider major groove.^[4]

History

The double-helix model of DNA structure was first published in the journal *Nature* by James D. Watson and Francis Crick in 1953^[5], based upon the crucial X-ray diffraction image of DNA (labeled as "Photo 51") from Rosalind Franklin in 1952^[6], followed by her more clarified DNA image with Raymond Gosling^[7]^[8], Maurice Wilkins, Alexander Stokes, and Herbert Wilson^[9], as well as base-pairing chemical and biochemical information by Erwin Chargaff^[10]^[11]^[12]^[13]^[14]^[15]. The previous model was triple-stranded DNA.

Crick, Wilkins, and Watson each received one third of the 1962 Nobel Prize in Physiology or Medicine for their contributions to the discovery.^[16] (Franklin, whose breakthrough X-ray diffraction data was used to formulate the DNA structure, died in 1958, and thus was ineligible to be nominated for a Nobel Prize.)



Nucleic acid hybridization

Hybridization is the process of complementary base pairs binding to form a double helix. Melting is the process by which the interactions between the strands of the double helix are broken, separating the two nucleic acid strands. These bonds are weak, easily separated by gentle heating, enzymes, or physical force. Melting occurs preferentially at certain points in the nucleic acid.^[17] **T** and **A** rich sequences are more easily melted than **C** and **G** rich regions. Particular base steps are also susceptible to DNA melting, particularly **T A** and **T G** base steps.^[18] These mechanical features are reflected by the use of sequences such as **TATAA** at the start of many genes to assist RNA polymerase in melting the DNA for transcription.

Strand separation by gentle heating, as used in PCR, is simple providing the molecules have fewer than about 10,000 base pairs (10 kilobase pairs, or 10 kbp). The intertwining of the DNA strands makes long segments difficult to separate. The cell avoids this problem by allowing its DNA-melting enzymes (helicases) to work concurrently with topoisomerases, which can chemically cleave the phosphate backbone of one of the strands so that it can swivel around the other. Helicases unwind the strands to facilitate the advance of sequence-reading enzymes such as DNA polymerase.



Two complementary regions of nucleic acid molecules will bind and form a double helical structure held together by base pairs.

Base pair geometry

The geometry of a base, or base pair step can be characterized by 6 coordinates: Shift, slide, rise, tilt, roll, and twist. These values precisely define the location and orientation in space of every base or base pair in a nucleic acid molecule relative to its predecessor along the axis of the helix. Together, they characterize the helical structure of the molecule. In regions of DNA or RNA where the "normal" structure is disrupted, the change in these values can be used to describe such disruption.

For each base pair, considered relative to its predecessor, there are the following base pair geometries to consider^[19] [20] [21] .

Shear

Stretch

Stagger

Buckle

Propeller twist

rotation of one base with respect to the other in the same base pair.

Opening

Shift

displacement along an axis in the base-pair plane perpendicular to the first, directed from the minor to the major groove.

Slide

displacement along an axis in the plane of the base pair directed from one strand to the other.

Rise

displacement along the helix axis.

Tilt

rotation around this axis.

vRoll

rotation around this axis.

Twist

rotation around the helix axis.

vx-displacement

y-displacement

inclination

tip

pitch

the number of base pairs per complete turn of the helix.

Rise and twist determine the handedness and pitch of the helix. The other coordinates, by contrast, can be zero. Slide and shift are typically small in B-DNA, but are substantial in A- and Z-DNA. Roll and tilt make successive base pairs less parallel, and are typically small. A diagram ^[22] of these coordinates can be found in 3DNA ^[23] website.

Note that "tilt" has often been used differently in the scientific literature, referring to the deviation of the first, inter-strand base-pair axis from perpendicularity to the helix axis. This corresponds to slide between a succession of base pairs, and in helix-based coordinates is properly termed "inclination".

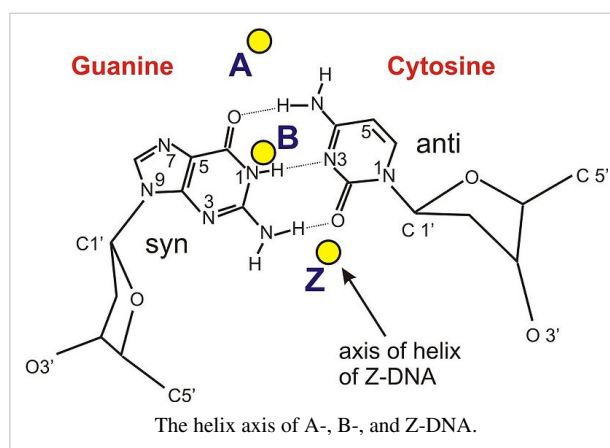
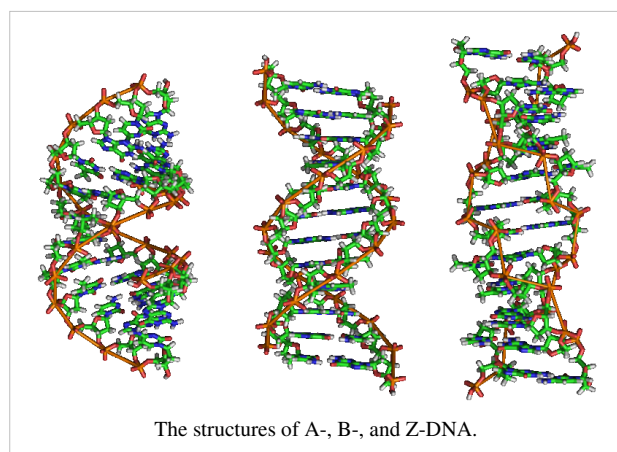
DNA helix geometries

Three DNA conformations are believed to be found in nature, A-DNA, B-DNA, and Z-DNA. The "B" form described by James D. Watson and Francis Crick is believed to predominate in cells^[24]. It is 23.7 Å wide and extends 34 Å per 10 bp of sequence. The double helix makes one complete turn about its axis every 10.4-10.5 base pairs in solution. This frequency of twist (known as the helical *pitch*) depends largely on stacking forces that each base exerts on its neighbours in the chain.

Other conformations are possible; A-DNA, B-DNA, C-DNA, E-DNA^[25], L-DNA (the enantiomeric form of D-DNA)^[26], P-DNA^[27], S-DNA, Z-DNA, etc. have been described so far.^[28] In fact, only the letters F, Q, U, V, and Y are now available to describe any new DNA structure that may appear in the future.^[29] ^[30] However, most of these forms have been created synthetically and have not been observed in naturally occurring biological systems. Also note the triple-stranded DNA possibility.

A- and Z-DNA

A-DNA and Z-DNA differ significantly in their geometry and dimensions to B-DNA, although still form helical structures. The A form appears likely to occur only in dehydrated samples of DNA, such as those used in crystallographic experiments, and possibly in hybrid pairings of DNA and RNA strands. Segments of DNA that cells have methylated for regulatory purposes may adopt the Z geometry, in which the strands turn about the helical axis the opposite way to A-DNA and B-DNA. There is also evidence of protein-DNA complexes forming Z-DNA structures.



Structural features of the three major forms of DNA

Geometry attribute	A-DNA	B-DNA	Z-DNA
Helix sense	right-handed	right-handed	left-handed
Repeating unit	1 bp	1 bp	2 bp
Rotation/bp	32.7°	35.9°	60°/2
bp/turn	11	10.5	12
Inclination of bp to axis	+19°	-1.2°	-9°
Rise/bp along axis	2.3 Å (0.23 nm)	3.32 Å (0.332 nm)	3.8 Å (0.38 nm)
Pitch/turn of helix	28.2 Å (2.82 nm)	33.2 Å (3.32 nm)	45.6 Å (4.56 nm)
Mean propeller twist	+18°	+16°	0°
Glycosyl angle	anti	anti	C: anti, G: syn
Sugar pucker	C3'-endo	C2'-endo	C: C2'-endo, G: C2'-exo
Diameter	23 Å (2.3 nm)	20 Å (2.0 nm)	18 Å (1.8 nm)
Sources: [31] [32] [33]			

Supercoiled DNA

The B form of the DNA helix twists 360° per 10.4-10.5 bp in the absence of torsional strain. But many molecular biological processes can induce torsional strain. A DNA segment with excess or insufficient helical twisting is referred to, respectively, as positively or negatively "supercoiled". DNA *in vivo* is typically negatively supercoiled, which facilitates the unwinding (melting) of the double-helix required for RNA transcription.

Non-helical forms

Other non-double helical forms of DNA have been described, for example side-by-side (SBS) and triple helical configurations. Single stranded DNA may exist *in statu nascendi* or as thermally induced despiralized DNA.

DNA bending

DNA is a relatively rigid polymer, typically modelled as a worm-like chain. It has three significant degrees of freedom; bending, twisting and compression, each of which cause particular limitations on what is possible with DNA within a cell. Twisting/torsional stiffness is important for the circularisation of DNA and the orientation of DNA bound proteins relative to each other and bending/axial stiffness is important for DNA wrapping and circularisation and protein interactions. Compression/extension is relatively unimportant in the absence of high tension.

Persistence length/Axial stiffness

Example sequences and their persistence lengths (B DNA)

Sequence	Persistence Length /base pairs
Random	154±10
(CA) _{repeat}	133±10
(CAG) _{repeat}	124±10
(TATA) _{repeat}	137±10

DNA in solution does not take a rigid structure but is continually changing conformation due to thermal vibration and collisions with water molecules, which makes classical measures of rigidity impossible. Hence, the bending stiffness of DNA is measured by the persistence length, defined as:

"The length of DNA over which the time-averaged orientation of the polymer becomes uncorrelated by a factor of e ".

This value may be directly measured using an atomic force microscope to directly image DNA molecules of various lengths. In an aqueous solution, the average persistence length is 46-50 nm or 140-150 base pairs (the diameter of DNA is 2 nm), although can vary significantly. This makes DNA a moderately stiff molecule.

The persistence length of a section of DNA is somewhat dependent on its sequence, and this can cause significant variation. The variation is largely due to base stacking energies and the residues which extend into the minor and major grooves.

Models for DNA bending

Stacking stability of base steps (B DNA)^[34]

Step	Stacking ΔG /kcal mol ⁻¹
T A	-0.19
T G or C A	-0.55
C G	-0.91
A G or C T	-1.06
A A or T T	-1.11
A T	-1.34

G A or T C	-1.43
C C or G G	-1.44
A C or G T	-1.81
G C	-2.17

The entropic flexibility of DNA is remarkably consistent with standard polymer physics models such as the *Kratky-Porod* worm-like chain model. Consistent with the worm-like chain model is the observation that bending DNA is also described by Hooke's law at very small (sub-piconewton) forces. However for DNA segments less than the persistence length, the bending force is approximately constant and behaviour deviates from the worm-like chain predictions.

This effect results in unusual ease in circularising small DNA molecules and a higher probability of finding highly bent sections of DNA.

Bending preference

DNA molecules often have a preferred direction to bend, ie. anisotropic bending. This is, again, due to the properties of the bases which make up the DNA sequence - a random sequence will have no preferred bend direction, i.e. isotropic bending.

Preferred DNA bend direction is determined by the stability of stacking each base on top of the next. If unstable base stacking steps are always found on one side of the DNA helix then the DNA will preferentially bend away from that direction. As bend angle increases then steric hindrances and ability to roll the residues relative to each other also play a role, especially in the minor groove. **A** and **T** residues will be preferentially be found in the minor grooves on the inside of bends. This effect is particularly seen in DNA-protein binding where tight DNA bending is induced, such as in nucleosome particles. See base step distortions above.

DNA molecules with exceptional bending preference can become intrinsically bent. This was first observed in trypanosomatid kinetoplast DNA. Typical sequences which cause this contain stretches of 4-6 **T** and **A** residues separated by **G** and **C** rich sections which keep the A and T residues in phase with the minor groove on one side of the molecule. For example:

G	A	T	T	C	C	A	A	A	A	T	G	T	C	A	A	A	A	A	T	A	G	G	C	A	A	A	A	A	T	G	C	C	A	A	A	A	A	T	C	C	C	A	A	C

The intrinsically bent structure is induced by the 'propeller twist' of base pairs relative to each other allowing unusual bifurcated Hydrogen-bonds between base steps. At higher temperatures this structure, and so the intrinsic bend, is lost.

All DNA which bends anisotropically has, on average, a longer persistence length and greater axial stiffness. This increased rigidity is required to prevent random bending which would make the molecule act isotropically.

DNA circularization

DNA circularization depends on both the axial (bending) stiffness and torsional (rotational) stiffness of the molecule. For a DNA molecule to successfully circularize it must be long enough to easily bend into the full circle and must have the correct number of bases so the ends are in the correct rotation to allow bonding to occur. The optimum length for circularization of DNA is around 400 base pairs (136 nm), with an integral number of turns of the DNA helix, i.e. multiples of 10.4 base pairs. Having a non integral number of turns presents a significant energy barrier for circularization, for example a $10.4 \times 30 = 312$ base pair molecule will circularize hundreds of times faster than $10.4 \times 30.5 \approx 317$ base pair molecule.

DNA stretching

Longer stretches of DNA are entropically elastic under tension. When DNA is in solution, it undergoes continuous structural variations due to the energy available in the thermal bath of the solvent. This is due to the thermal vibration of the molecule combined with continual collisions with water molecules. For entropic reasons, more compact relaxed states are thermally accessible than stretched out states, and so DNA molecules are almost universally found in a tangled relaxed layouts. For this reason, a single molecule of DNA will stretch under a force, straightening it out. Using optical tweezers, the entropic stretching behavior of DNA has been studied and analyzed from a polymer physics perspective, and it has been found that DNA behaves largely like the *Kratky-Porod* worm-like chain model under physiologically accessible energy scales.

Under sufficient tension and positive torque, DNA is thought to undergo a phase transition with the bases splaying outwards and the phosphates moving to the middle. This proposed structure for overstretched DNA has been called "P-form DNA," in honor of Linus Pauling who originally presented it as a possible structure of DNA^[27]

The mechanical properties DNA under compression have not been characterized due to experimental difficulties in preventing the polymer from bending under the compressive force.

DNA topology

Within the cell most DNA is topologically restricted. DNA is typically found in closed loops (such as plasmids in prokaryotes) which are topologically closed, or as very long molecules whose diffusion coefficients produce effectively topologically closed domains. Linear sections of DNA are also commonly bound to proteins or physical structures (such as membranes) to form closed topological loops.

Francis Crick was one of the first to propose the importance of linking numbers when considering DNA supercoils. In a paper published in 1976, Crick outlined the problem as follows:

In considering supercoils formed by closed double-stranded molecules of DNA certain mathematical concepts, such as the linking number and the twist, are needed. The meaning of these for a closed ribbon is explained and also that of the writhing number of a closed curve. Some simple examples are given, some of which may be relevant to the structure of chromatin.^[35]

Analysis of DNA topology uses three values:

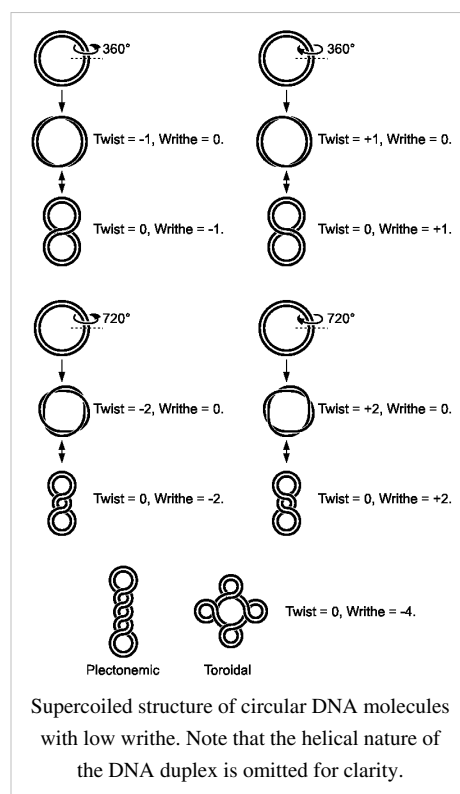
L = linking number - the number of times one DNA strand wraps around the other. It is an integer for a closed loop and constant for a closed topological domain.

T = twist - total number of turns in the double stranded DNA helix. This will normally tend to approach the number of turns that a topologically open double stranded DNA helix makes free in solution: number of bases/10.5, assuming there are no intercalating agents (e.g., chloroquine) or other elements modifying the stiffness of the DNA.

W = writhe - number of turns of the double stranded DNA helix around the superhelical axis

$$L = T + W \text{ and } \Delta L = \Delta T + \Delta W$$

Any change of T in a closed topological domain must be balanced by a change in W , and vice versa. This results in higher order structure of DNA. A circular DNA molecule with a writhe of 0 will be circular. If the twist of this



molecule is subsequently increased or decreased by supercoiling then the writhe will be appropriately altered, making the molecule undergo plectonemic or toroidal superhelical coiling.

When the ends of a piece of double stranded helical DNA are joined so that it forms a circle the strands are topologically knotted. This means the single strands cannot be separated any process that does not involve breaking a strand (such as heating). The task of un-knotting topologically linked strands of DNA falls to enzymes known as topoisomerases. These enzymes are dedicated to un-knotting circular DNA by cleaving one or both strands so that another double or single stranded segment can pass through. This un-knotting is required for the replication of circular DNA and various types of recombination in linear DNA which have similar topological constraints.

The linking number paradox

For many years, the origin of residual supercoiling in eukaryotic genomes remained unclear. This topological puzzle was referred to by some as the "linking number paradox".^[36] However, when experimentally determined structures of the nucleosome displayed an overtwisted left-handed wrap of DNA around the histone octamer^{[37] [38]}, this "paradox" was solved.

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Triple-stranded DNA

A **TNA** is a structure of DNA in which three oligonucleotides wind around each other and form a triple helix. In this structure, one strand binds to a B-form DNA double helix through Hoogsteen or reversed Hoogsteen hydrogen bonds.

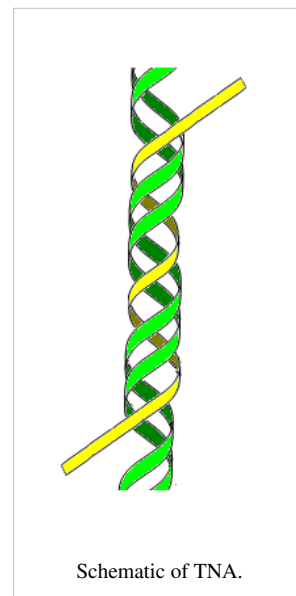
For example, a nucleobase T binds to a Watson-Crick base-pairing of T-A by Hoogsteen hydrogen bonds between an A $\times$ T pair (x represents a Hoogsteen base pair). An N-3 protonated cytosine, represented as C $^{+}$, can also form a base-triplet with a C-G pair through the Hoogsteen base-pairing of an G $\times$ C $^{+}$. Thus, the triple-helical DNAs using these Hoogsteen pairings consist of two homopyrimidines and one homopurine, and the homopyrimidine third strand is parallel to the homopurine strand.

A homopurine third strand can also bind to a homopurine-homopyrimidine duplex using reversed Hoogsteen patterns. In this triplex, a nucleobase A binds to a T-A base pair and a G to a C-G pair. Since the nucleobases on the third strand have to be reversed, the homopurine third strand is antiparallel to the homopurine strand of the original duplex.

Triple-stranded DNA was a common hypothesis in the 1950s when scientists were struggling to discover DNA's true structural form. Watson and Crick (who later won the Nobel Prize for their double-helix model) originally considered a triple-helix model, as did Pauling and Corey who published a proposal for their triple-helix model in the 1953 scientific journal *Nature*, as well as fellow scientist Fraser. However, Watson and Crick soon identified several problems with these models: 1) Negatively charged phosphates near the axis will repel each other, leaving the question as to how the three-chain structure would stay together. 2) In a triple-helix model (specifically Pauling and Corey's model), some of the van der Waals distances appear to be too small. Fraser's model differed from Pauling and Corey's in that in his model the phosphates are on the outside and the bases are on the inside, linked together by hydrogen bonds. However, Watson and Crick found Fraser's model to be too ill-defined to comment specifically on its inadequacies in their publication in "Nature" (1953): Molecular Structure of Nucleic Acids.

Triple-stranded DNA was also described in 1957, when it was thought to occur in only one *in vivo* biological process: as an intermediate product during the action of the *E. coli* recombination enzyme RecA. Its role in that process is not understood.

Using nucleic acid segments that bind to the DNA duplexes to form triple strands as a way of regulating gene expression is under investigation by biotechnology companies. Similar work is also being undertaken at Yale University.



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G-quadruplex

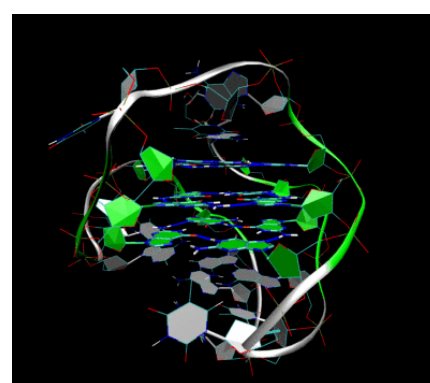
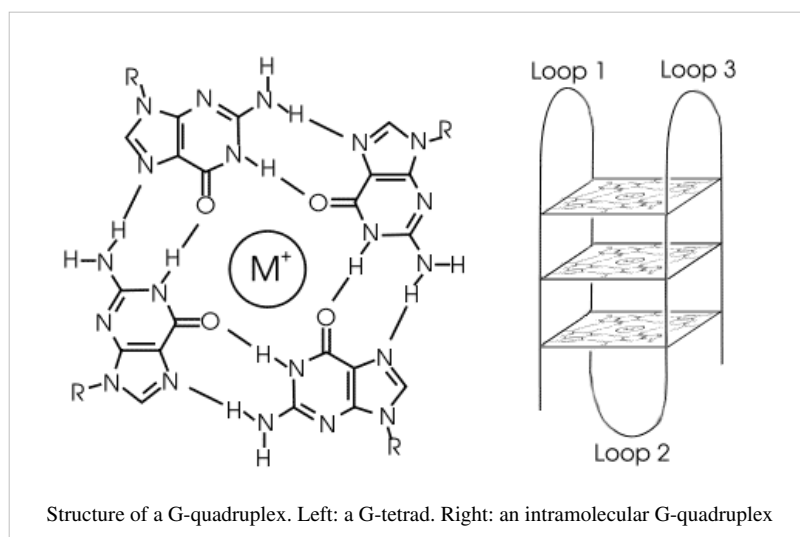
Nucleic acid sequences which are rich in guanine are capable of forming four-stranded structures called **G-quadruplexes** (also known as **G-tetrads** or **G₄-DNA**). These consist of a square arrangement of guanines (a tetrad), stabilized by Hoogsteen hydrogen bonding. They are further stabilized by the existence of a monovalent cation (especially potassium) in the center of the tetrads. They can be formed of DNA, RNA, LNA, and PNA, and may be intramolecular, bimolecular, or tetramolecular. Depending on the direction of the strands or parts of a strand that form the tetrads, structures may be described as parallel or antiparallel.

Telomeric quadruplexes

Telomeric repeats in a variety of organisms have been shown to form these structures *in vitro*, and they have also been shown to form *in vivo* in some cases. The human telomeric repeat (which is the same for all vertebrates) consists of many repeats of the sequence d(GGTTAG), and the quadruplexes formed by this structure have been well studied by NMR and X-ray crystal structure determination. The formation of these quadruplexes in telomeres has been shown to decrease the activity of the enzyme telomerase, which is responsible for maintaining length of telomeres and is involved in around 85% of all cancers. This is an active target of drug discovery.

Non-telomeric quadruplexes

Recently, there has been increasing interest in quadruplexes in locations other than at the telomere. This was given a large boost by the work by Simonsson [1] and Hurley [2] on the proto-oncogene c-myc, which was



3D Structure of the intramolecular human telomeric G-quadruplex in potassium solution (PDB ID 2HY9). The backbone is represented by a tube. The center of this structure contains three layers of G-tetrads. The hydrogen bonds in these layers are represented by blue dashed lines.

shown to form a quadruplex in a nuclease hypersensitive region critical for gene activity. Since then, many other genes have been shown to have G-quadruplexes in their promoter regions, including the chicken β -globin gene, human ubiquitin-ligase RFP2 and the proto-oncogenes c-kit, bcl-2, VEGF, H-ras and N-ras. This list is ever-increasing.

Genome-wide surveys based on a quadruplex folding rule have been performed, which have identified 376,000 Putative Quadruplex Sequences (PQS) in the human genome, although not all of these probably form *in vivo*. [3] A similar study has identified putative G-quadruplexes in prokaryotes [4]. There are several possible models for how quadruplexes could control gene activity, either by upregulation or downregulation. One model is shown below, with G-quadruplex formation in or near a promoter blocking transcription of the gene, and hence de-activating it. In another model, quadruplex formed at the non-coding DNA strand helps to maintain an open conformation of the coding DNA strand and enhance an expression of the respective gene.

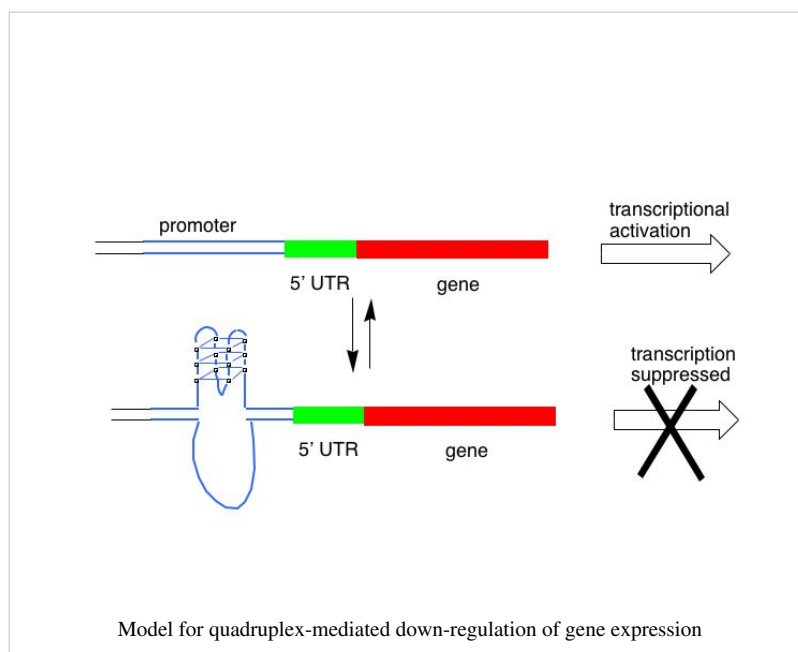
Ligands which bind quadruplexes

One way of inducing or stabilizing G-quadruplex formation, is to introduce a molecule which can bind to the G-quadruplex structure, and a number of ligands, both small molecules and proteins, have been developed which can do so. This has become an increasingly large field of research.

A number of naturally occurring proteins have been identified which selectively bind to G-quadruplexes. These include the helicases implicated in Bloom's and Werner's syndromes

and the *Saccharomyces cerevisiae* protein RAP1. An artificially derived three zinc finger protein called Gq1, which is specific for G-quadruplexes has also been developed, as have specific antibodies.

Cationic porphyrins have been shown to bind intercalatively with G-quadruplexes, as well as the molecule telomestatin.



Quadruplex prediction techniques

Identifying and predicting sequences which have the capacity to form quadruplexes is an important tool in further understanding of their role. A rule for predicting the formation has been proposed, where sequences are predicted to fold based on the pattern $d(G_{3+}N_{1-7}G_{3+}N_{1-7}G_{3+}N_{1-7}G_{3+})$, where N is any base (including guanine). This rule has been widely used in on-line algorithms.

External links

Books

- Neidle & Balasubramanian, ed (2006). *Quadruplex Nucleic Acids* ^[5]. ISBN 0-85404-374-8.

Quadruplex websites

- Quadruplex.org^[6] - a website to serve the quadruplex community
- Quadbase^[7] - downloadable data on predicted G-quadruplexes
- Greglist^[8] - a database listing potential G-quadruplex regulated genes
- Database on Quadruplex information: QuadBase from IGIB^[9]
- GRSDb^[10] - a database of G-quadruplexes near RNA processing sites.
- GRS_UTRdb^[11] - a database of G-quadruplexes in the UTRs.
- G-quadruplex Resource Site^[12]

Research papers

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Tools to predict G-quadruplex motifs

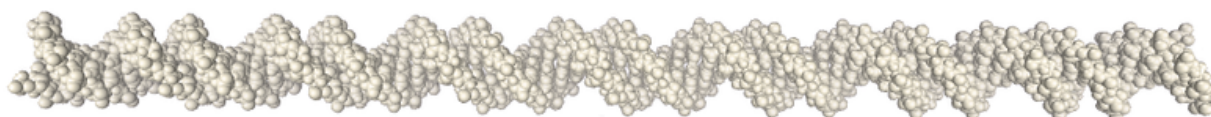
- Quadparser: Downloadable program for finding putative quadruplex-forming sequences^[17]
- QGRS Mapper: a web-based application for predicting G-quadruplexes in nucleotide sequences and NCBI genes^[18]
- Quadfinder: Tool for Prediction and Analysis of G Quadruplex Motifs in DNA/RNA Sequences from IGIB^[19]

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- [4] <http://www.genome.org/cgi/content/short/16/5/644>
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List of nucleic acid simulation software



This is a list of computer programs that are used for nucleic acids simulations.

Min - Optimization, **MD** - Molecular dynamics, **MC** - Monte Carlo, **REM** - Replica exchange method,

Crt - Cartesian coordinates. **Int** - Internal coordinates **Exp** - Explicit water. **Imp** - Implicit water.

Lig - Ligands interactions. **HA** - Hardware accelerated.

Name	View 3D	Model Build	Min	MD	MC	REM	Crt	Int	Exp	Imp	Lig	HA	Comments	License	Homepage
Abalone	+	+	+	+	+	+	+		+	+	+	+	DNA, proteins, ligands	Free	Agile Molecule ^[1]
AMBER ^[2]		+	+	+		+	+		+	+	+		AMBER Force Field	Commercial	ambermd.org ^[3]
Ascalaph Designer	+	+	+	+			+		+	+	+		AMBER	GPL	biomolecular-modeling.com ^[4]
CHARMM		+	+	+	+		+		+	+	+		CHARMM Force Field	Commercial	charmm.org ^[5]
ICM ^[6]	+	+	+		+			+		+			Global optimization	Commercial	Molsoft ^[7]
JUMNA ^[8]		+	+					+		+				Commercial	
MDynaMix ^[9]	+	+		+			+		+		+		Common MD	GPL	Stockholm University ^[10]
MOE	+	+	+	+			+		+		+		Molecular Operating Environment	Commercial	Chemical Computing Group ^[11]
NAB ^[12]		+											Nucleic Acid Builder	GPL	New Jersey University ^[13]
NAMD	+		+	+			+		+		+	+	NANoscale Molecular Dynamics	Free	University of Illinois ^[14]

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Molecular dynamics

Molecular dynamics (MD) is a form of computer simulation in which atoms and molecules are allowed to interact for a period of time by approximations of known physics, giving a view of the motion of the particles. Molecular dynamics simulation is frequently used in the study of proteins and biomolecules, as well as in materials science. It is tempting, though not entirely accurate, to describe the technique as a "virtual microscope" with high temporal and spatial resolution. Whereas it is possible to take "still snapshots" of crystal structures and probe features of the motion of molecules through NMR, no current experimental technique allows access to all the time scales of motion with atomic resolution. Richard Feynman once said that "If we were to name the most powerful assumption of all, which leads one on and on in an attempt to understand life, it is that all things are made of atoms, and that everything that living things do can be understood in terms of the jiggings and wiggings of atoms." Molecular dynamics lets scientists peer into the motion of individual atoms in a way which is not possible in laboratory experiments.

Molecular dynamics is a specialized discipline of molecular modeling and computer simulation based on statistical mechanics; the main justification of the MD method is that statistical ensemble averages are equal to time averages of the system, known as the ergodic hypothesis. MD has also been termed "statistical mechanics by numbers" and "Laplace's vision of Newtonian mechanics" of predicting the future by animating nature's forces^{[1] [2]} and allowing insight into molecular motion on an atomic scale. However, long MD simulations are mathematically ill-conditioned, generating cumulative errors in numerical integration that can be minimized with proper selection of algorithms and parameters, but not eliminated entirely. Furthermore, current potential energy functions (also called force-fields) are, in many cases, not sufficiently accurate to reproduce the dynamics of molecular systems, so the much more computationally demanding *Ab Initio* Molecular Dynamics method must be used. Nevertheless, molecular dynamics techniques allow detailed time and space resolution into representative behavior in phase space for carefully selected systems.

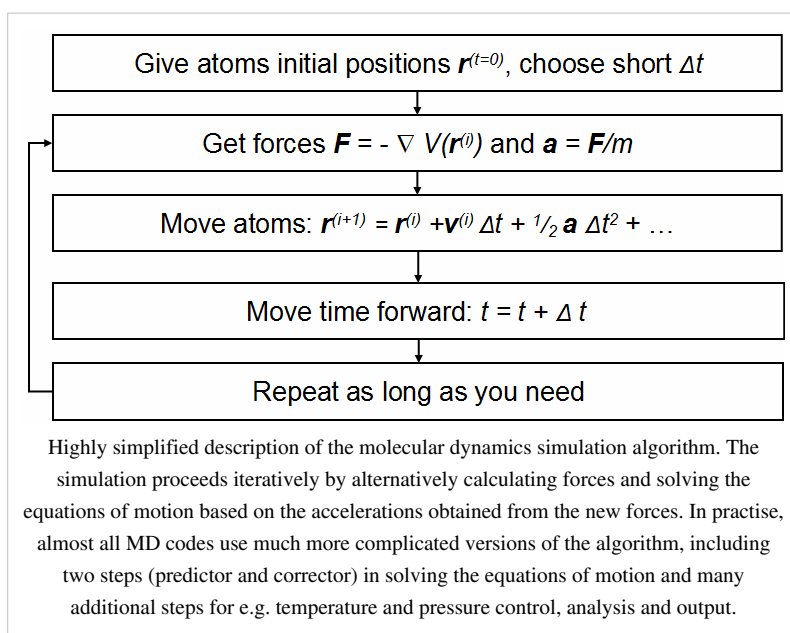
Before it became possible to simulate molecular dynamics with computers, some undertook the hard work of trying it with physical models such as macroscopic spheres. The idea was to arrange them to replicate the properties of a liquid. J.D. Bernal said, in 1962: "... I took a number of rubber balls and stuck them together with rods of a selection of different lengths ranging from 2.75 to 4 inches. I tried to do this in the first place as casually as possible, working in my own office, being interrupted every five minutes or so and not remembering what I had done before the

interruption."^[3] Fortunately, now computers keep track of bonds during a simulation.

Because molecular systems generally consist of a vast number of particles, it is in general impossible to find the properties of such complex systems analytically. When the number of particles interacting is higher than two, the result is chaotic motion (see n-body problem). MD simulation circumvents the analytical intractability by using numerical methods. It represents an interface between laboratory experiments and theory, and can be understood as a "virtual experiment". MD probes the relationship between molecular structure, movement and function. Molecular dynamics is a multidisciplinary method. Its laws and theories stem from mathematics, physics, and chemistry, and it employs algorithms from computer science and information theory. It was originally conceived within theoretical physics in the late 1950s^[4] and early 1960s^[5], but is applied today mostly in materials science and the modeling of biomolecules.

Areas of Application

There is a significant difference between the focus and methods used by chemists and physicists, and this is reflected in differences in the jargon used by the different fields. In chemistry and biophysics, the interaction between the particles is either described by a "force field" (**classical MD**), a quantum chemical model, or a mix between the two. These terms are not used in physics, where the interactions are usually described by the name of the theory or approximation being used and called the potential energy, or just the "potential".



Beginning in theoretical physics, the method of MD gained popularity in materials science and since the 1970s also in biochemistry and biophysics. In chemistry, MD serves as an important tool in protein structure determination and refinement using experimental tools such as X-ray crystallography and NMR. It has also been applied with limited success as a method of refining protein structure predictions. In physics, MD is used to examine the dynamics of atomic-level phenomena that cannot be observed directly, such as thin film growth and ion-subplantation. It is also used to examine the physical properties of nanotechnological devices that have not or cannot yet be created.

In applied mathematics and theoretical physics, molecular dynamics is a part of the research realm of dynamical systems, ergodic theory and statistical mechanics in general. The concepts of energy conservation and molecular entropy come from thermodynamics. Some techniques to calculate conformational entropy such as principal components analysis come from information theory. Mathematical techniques such as the transfer operator become applicable when MD is seen as a Markov chain. Also, there is a large community of mathematicians working on volume preserving, symplectic integrators for more computationally efficient MD simulations.

MD can also be seen as a special case of the discrete element method (DEM) in which the particles have spherical shape (e.g. with the size of their van der Waals radii.) Some authors in the DEM community employ the term MD rather loosely, even when their simulations do not model actual molecules.

Design Constraints

Design of a molecular dynamics simulation should account for the available computational power. Simulation size (n =number of particles), timestep and total time duration must be selected so that the calculation can finish within a reasonable time period. However, the simulations should be long enough to be relevant to the time scales of the natural processes being studied. To make statistically valid conclusions from the simulations, the time span simulated should match the kinetics of the natural process. Otherwise, it is analogous to making conclusions about how a human walks from less than one footstep. Most scientific publications about the dynamics of proteins and DNA use data from simulations spanning nanoseconds ($1\text{E-}9$ s) to microseconds ($1\text{E-}6$ s). To obtain these simulations, several CPU-days to CPU-years are needed. Parallel algorithms allow the load to be distributed among CPUs; an example is the spatial or force decomposition algorithm [6].

During a classical MD simulation, the most CPU intensive task is the evaluation of the potential (force field) as a function of the particles' internal coordinates. Within that energy evaluation, the most expensive one is the non-bonded or non-covalent part. In Big O notation, common molecular dynamics simulations scale by $O(n^2)$ if all pair-wise electrostatic and van der Waals interactions must be accounted for explicitly. This computational cost can be reduced by employing electrostatics methods such as Particle Mesh Ewald ($O(n \log(n))$), P3M or good spherical cutoff techniques ($O(n)$).

Another factor that impacts total CPU time required by a simulation is the size of the integration timestep. This is the time length between evaluations of the potential. The timestep must be chosen small enough to avoid discretization errors (i.e. smaller than the fastest vibrational frequency in the system). Typical timesteps for classical MD are in the order of 1 femtosecond ($1\text{E-}15$ s). This value may be extended by using algorithms such as SHAKE, which fix the vibrations of the fastest atoms (e.g. hydrogens) into place. Multiple time scale methods have also been developed, which allow for extended times between updates of slower long-range forces.^{[7] [8] [9]}

For simulating molecules in a solvent, a choice should be made between explicit solvent and implicit solvent. Explicit solvent particles (such as the TIP3P, SPC/E and SPC-f water models) must be calculated expensively by the force field, while implicit solvents use a mean-field approach. Using an explicit solvent is computationally expensive, requiring inclusion of roughly ten times more particles in the simulation. But the granularity and viscosity of explicit solvent is essential to reproduce certain properties of the solute molecules. This is especially important to reproduce kinetics.

In all kinds of molecular dynamics simulations, the simulation box size must be large enough to avoid boundary condition artifacts. Boundary conditions are often treated by choosing fixed values at the edges (which may cause artifacts), or by employing periodic boundary conditions in which one side of the simulation loops back to the opposite side, mimicking a bulk phase.

Microcanonical ensemble (NVE)

In the **microcanonical**, or **NVE** ensemble, the system is isolated from changes in moles (N), volume (V) and energy (E). It corresponds to an adiabatic process with no heat exchange. A microcanonical molecular dynamics trajectory may be seen as an exchange of potential and kinetic energy, with total energy being conserved. For a system of N particles with coordinates $\mathbf{X}$ and velocities $\mathbf{V}$, the following pair of first order differential equations may be written in Newton's notation as

$$\mathbf{F}(\mathbf{X}) = -\nabla U(\mathbf{X}) = M\dot{\mathbf{V}}(t)$$

$$\mathbf{V}(t) = \dot{\mathbf{X}}(t).$$

The potential energy function $U(\mathbf{X})$ of the system is a function of the particle coordinates $\mathbf{X}$. It is referred to simply as the "potential" in Physics, or the "force field" in Chemistry. The first equation comes from Newton's laws; the force $\mathbf{F}$ acting on each particle in the system can be calculated as the negative gradient of $U(\mathbf{X})$.

For every timestep, each particle's position $\mathbf{X}$ and velocity $\mathbf{V}$ may be integrated with a symplectic method such as Verlet. The time evolution of $\mathbf{X}$ and $\mathbf{V}$ is called a trajectory. Given the initial positions (e.g. from theoretical knowledge) and velocities (e.g. randomized Gaussian), we can calculate all future (or past) positions and velocities.

One frequent source of confusion is the meaning of temperature in MD. Commonly we have experience with macroscopic temperatures, which involve a huge number of particles. But temperature is a statistical quantity. If there is a large enough number of atoms, statistical temperature can be estimated from the *instantaneous temperature*, which is found by equating the kinetic energy of the system to $nk_{\text{B}}T/2$ where n is the number of degrees of freedom of the system.

A temperature-related phenomenon arises due to the small number of atoms that are used in MD simulations. For example, consider simulating the growth of a copper film starting with a substrate containing 500 atoms and a deposition energy of 100 eV. In the real world, the 100 eV from the deposited atom would rapidly be transported through and shared among a large number of atoms ($\sim 10^{10}$ or more) with no big change in temperature. When there are only 500 atoms, however, the substrate is almost immediately vaporized by the deposition. Something similar happens in biophysical simulations. The temperature of the system in NVE is naturally raised when macromolecules such as proteins undergo exothermic conformational changes and binding.

Canonical ensemble (NVT)

In the canonical ensemble, moles (N), volume (V) and temperature (T) are conserved. It is also sometimes called constant temperature molecular dynamics (CTMD). In NVT, the energy of endothermic and exothermic processes is exchanged with a thermostat.

A variety of thermostat methods is available to add and remove energy from the boundaries of an MD system in a more or less realistic way, approximating the canonical ensemble. Popular techniques to control temperature include velocity rescaling, the Nosé-Hoover thermostat, Nosé-Hoover chains, the Berendsen thermostat and Langevin dynamics. Note that the Berendsen thermostat might introduce the flying ice cube effect, which leads to unphysical translations and rotations of the simulated system.

It is not trivial to obtain a canonical distribution of conformations and velocities using these algorithms. How this depends on system size, thermostat choice, thermostat parameters, time step and integrator is the subject of many articles in the field.

Isothermal-Isobaric (NPT) ensemble

In the isothermal-isobaric ensemble, moles (N), pressure (P) and temperature (T) are conserved. In addition to a thermostat, a barostat is needed. It corresponds most closely to laboratory conditions with a flask open to ambient temperature and pressure.

In the simulation of biological membranes, isotropic pressure control is not appropriate. For lipid bilayers, pressure control occurs under constant membrane area (NPAT) or constant surface tension " γ " (NP γ T).

Generalized ensembles

The replica exchange method is a generalized ensemble. It was originally created to deal with the slow dynamics of disordered spin systems. It is also called parallel tempering. The replica exchange MD (REMD) formulation^[10] tries to overcome the multiple-minima problem by exchanging the temperature of non-interacting replicas of the system running at several temperatures.

Potentials in MD simulations

A molecular dynamics simulation requires the definition of a potential function, or a description of the terms by which the particles in the simulation will interact. In chemistry and biology this is usually referred to as a force field. Potentials may be defined at many levels of physical accuracy; those most commonly used in chemistry are based on molecular mechanics and embody a classical treatment of particle-particle interactions that can reproduce structural and conformational changes but usually cannot reproduce chemical reactions.

The reduction from a fully quantum description to a classical potential entails two main approximations. The first one is the Born-Oppenheimer approximation, which states that the dynamics of electrons is so fast that they can be considered to react instantaneously to the motion of their nuclei. As a consequence, they may be treated separately. The second one treats the nuclei, which are much heavier than electrons, as point particles that follow classical Newtonian dynamics. In classical molecular dynamics the effect of the electrons is approximated as a single potential energy surface, usually representing the ground state.

When finer levels of detail are required, potentials based on quantum mechanics are used; some techniques attempt to create hybrid classical/quantum potentials where the bulk of the system is treated classically but a small region is treated as a quantum system, usually undergoing a chemical transformation.

Empirical potentials

Empirical potentials used in chemistry are frequently called force fields, while those used in materials physics are called just empirical or analytical potentials.

Most force fields in chemistry are empirical and consist of a summation of bonded forces associated with chemical bonds, bond angles, and bond dihedrals, and non-bonded forces associated with van der Waals forces and electrostatic charge. Empirical potentials represent quantum-mechanical effects in a limited way through ad-hoc functional approximations. These potentials contain free parameters such as atomic charge, van der Waals parameters reflecting estimates of atomic radius, and equilibrium bond length, angle, and dihedral; these are obtained by fitting against detailed electronic calculations (quantum chemical simulations) or experimental physical properties such as elastic constants, lattice parameters and spectroscopic measurements.

Because of the non-local nature of non-bonded interactions, they involve at least weak interactions between all particles in the system. Its calculation is normally the bottleneck in the speed of MD simulations. To lower the computational cost, force fields employ numerical approximations such as shifted cutoff radii, reaction field algorithms, particle mesh Ewald summation, or the newer Particle-Particle Particle Mesh (P3M).

Chemistry force fields commonly employ preset bonding arrangements (an exception being *ab-initio* dynamics), and thus are unable to model the process of chemical bond breaking and reactions explicitly. On the other hand, many of the potentials used in physics, such as those based on the bond order formalism can describe several different coordinations of a system and bond breaking. Examples of such potentials include the Brenner potential^[11] for hydrocarbons and its further developments for the C-Si-H and C-O-H systems. The ReaxFF potential^[12] can be considered a fully reactive hybrid between bond order potentials and chemistry force fields.

Pair potentials vs. many-body potentials

The potential functions representing the non-bonded energy are formulated as a sum over interactions between the particles of the system. The simplest choice, employed in many popular force fields, is the "pair potential", in which the total potential energy can be calculated from the sum of energy contributions between pairs of atoms. An example of such a pair potential is the non-bonded Lennard-Jones potential (also known as the 6-12 potential), used for calculating van der Waals forces.

$$U(r) = 4\epsilon \left[\left(\frac{\sigma}{r} \right)^{12} - \left(\frac{\sigma}{r} \right)^6 \right]$$

Another example is the Born (ionic) model of the ionic lattice. The first term in the next equation is Coulomb's law for a pair of ions, the second term is the short-range repulsion explained by Pauli's exclusion principle and the final term is the dispersion interaction term. Usually, a simulation only includes the dipolar term, although sometimes the quadrupolar term is included as well.

$$U_{ij}(r_{ij}) = \sum \frac{z_i z_j}{4\pi\epsilon_0} \frac{1}{r_{ij}} + \sum A_l \exp \frac{-r_{ij}}{p_l} + \sum C_l r_{ij}^{-n_l} + \dots$$

In many-body potentials, the potential energy includes the effects of three or more particles interacting with each other. In simulations with pairwise potentials, global interactions in the system also exist, but they occur only through pairwise terms. In many-body potentials, the potential energy cannot be found by a sum over pairs of atoms, as these interactions are calculated explicitly as a combination of higher-order terms. In the statistical view, the dependency between the variables cannot in general be expressed using only pairwise products of the degrees of freedom. For example, the Tersoff potential^[13], which was originally used to simulate carbon, silicon and germanium and has since been used for a wide range of other materials, involves a sum over groups of three atoms, with the angles between the atoms being an important factor in the potential. Other examples are the embedded-atom method (EAM)^[14] and the Tight-Binding Second Moment Approximation (TBSMA) potentials^[15], where the electron density of states in the region of an atom is calculated from a sum of contributions from surrounding atoms, and the potential energy contribution is then a function of this sum.

Semi-empirical potentials

Semi-empirical potentials make use of the matrix representation from quantum mechanics. However, the values of the matrix elements are found through empirical formulae that estimate the degree of overlap of specific atomic orbitals. The matrix is then diagonalized to determine the occupancy of the different atomic orbitals, and empirical formulae are used once again to determine the energy contributions of the orbitals.

There are a wide variety of semi-empirical potentials, known as tight-binding potentials, which vary according to the atoms being modeled.

Polarizable potentials

Most classical force fields implicitly include the effect of polarizability, e.g. by scaling up the partial charges obtained from quantum chemical calculations. These partial charges are stationary with respect to the mass of the atom. But molecular dynamics simulations can explicitly model polarizability with the introduction of induced dipoles through different methods, such as Drude particles or fluctuating charges. This allows for a dynamic redistribution of charge between atoms which responds to the local chemical environment.

For many years, polarizable MD simulations have been touted as the next generation. For homogenous liquids such as water, increased accuracy has been achieved through the inclusion of polarizability.^[16] Some promising results have also been achieved for proteins.^[17] However, it is still uncertain how to best approximate polarizability in a simulation.

***Ab-initio* methods**

In classical molecular dynamics, a single potential energy surface (usually the ground state) is represented in the force field. This is a consequence of the Born-Oppenheimer approximation. In excited states, chemical reactions or a more accurate representation is needed, electronic behavior can be obtained from first principles by using a quantum mechanical method, such as Density Functional Theory. This is known as Ab Initio Molecular Dynamics (AIMD). Due to the cost of treating the electronic degrees of freedom, the computational cost of this simulations is much higher than classical molecular dynamics. This implies that AIMD is limited to smaller systems and shorter periods of time.

Ab-initio quantum-mechanical methods may be used to calculate the potential energy of a system on the fly, as needed for conformations in a trajectory. This calculation is usually made in the close neighborhood of the reaction coordinate. Although various approximations may be used, these are based on theoretical considerations, not on empirical fitting. *Ab-Initio* calculations produce a vast amount of information that is not available from empirical methods, such as density of electronic states or other electronic properties. A significant advantage of using *ab-initio* methods is the ability to study reactions that involve breaking or formation of covalent bonds, which correspond to multiple electronic states.

A popular software for *ab-initio* molecular dynamics is the Car-Parrinello Molecular Dynamics (CPMD) package based on the density functional theory.

Hybrid QM/MM

QM (quantum-mechanical) methods are very powerful. However, they are computationally expensive, while the MM (classical or molecular mechanics) methods are fast but suffer from several limitations (require extensive parameterization; energy estimates obtained are not very accurate; cannot be used to simulate reactions where covalent bonds are broken/formed; and are limited in their abilities for providing accurate details regarding the chemical environment). A new class of method has emerged that combines the good points of QM (accuracy) and MM (speed) calculations. These methods are known as mixed or hybrid quantum-mechanical and molecular mechanics methods (hybrid QM/MM). The methodology for such techniques was introduced by Warshel and coworkers. In the recent years have been pioneered by several groups including: Arieh Warshel (University of Southern California), Weitao Yang (Duke University), Sharon Hammes-Schiffer (The Pennsylvania State University), Donald Truhlar and Jiali Gao (University of Minnesota) and Kenneth Merz (University of Florida).

The most important advantage of hybrid QM/MM methods is the speed. The cost of doing classical molecular dynamics (MM) in the most straightforward case scales $O(n^2)$, where n is the number of atoms in the system. This is mainly due to electrostatic interactions term (every particle interacts with every other particle). However, use of cutoff radius, periodic pair-list updates and more recently the variations of the particle-mesh Ewald's (PME) method has reduced this between $O(n)$ to $O(n^2)$. In other words, if a system with twice as many atoms is simulated then it would take between two to four times as much computing power. On the other hand the simplest *ab-initio* calculations typically scale $O(n^3)$ or worse (Restricted Hartree-Fock calculations have been suggested to scale $\sim O(n^{2.7})$). To overcome the limitation, a small part of the system is treated quantum-mechanically (typically active-site of an enzyme) and the remaining system is treated classically.

In more sophisticated implementations, QM/MM methods exist to treat both light nuclei susceptible to quantum effects (such as hydrogens) and electronic states. This allows generation of hydrogen wave-functions (similar to electronic wave-functions). This methodology has been useful in investigating phenomena such as hydrogen tunneling. One example where QM/MM methods have provided new discoveries is the calculation of hydride transfer in the enzyme liver alcohol dehydrogenase. In this case, tunneling is important for the hydrogen, as it determines the reaction rate.^[18]

Coarse-graining and reduced representations

At the other end of the detail scale are coarse-grained and lattice models. Instead of explicitly representing every atom of the system, one uses "pseudo-atoms" to represent groups of atoms. MD simulations on very large systems may require such large computer resources that they cannot easily be studied by traditional all-atom methods. Similarly, simulations of processes on long timescales (beyond about 1 microsecond) are prohibitively expensive, because they require so many timesteps. In these cases, one can sometimes tackle the problem by using reduced representations, which are also called coarse-grained models.

Examples for coarse graining (CG) methods are discontinuous molecular dynamics (CG-DMD)^{[19] [20]} and Go-models^[21]. Coarse-graining is done sometimes taking larger pseudo-atoms. Such united atom approximations have been used in MD simulations of biological membranes. The aliphatic tails of lipids are represented by a few pseudo-atoms by gathering 2 to 4 methylene groups into each pseudo-atom.

The parameterization of these very coarse-grained models must be done empirically, by matching the behavior of the model to appropriate experimental data or all-atom simulations. Ideally, these parameters should account for both enthalpic and entropic contributions to free energy in an implicit way. When coarse-graining is done at higher levels, the accuracy of the dynamic description may be less reliable. But very coarse-grained models have been used successfully to examine a wide range of questions in structural biology.

Examples of applications of coarse-graining in biophysics:

- protein folding studies are often carried out using a single (or a few) pseudo-atoms per amino acid;
- DNA supercoiling has been investigated using 1-3 pseudo-atoms per basepair, and at even lower resolution;
- Packaging of double-helical DNA into bacteriophage has been investigated with models where one pseudo-atom represents one turn (about 10 basepairs) of the double helix;
- RNA structure in the ribosome and other large systems has been modeled with one pseudo-atom per nucleotide.

The simplest form of coarse-graining is the "united atom" (sometimes called "extended atom") and was used in most early MD simulations of proteins, lipids and nucleic acids. For example, instead of treating all four atoms of a CH₃ methyl group explicitly (or all three atoms of CH₂ methylene group), one represents the whole group with a single pseudo-atom. This pseudo-atom must, of course, be properly parameterized so that its van der Waals interactions with other groups have the proper distance-dependence. Similar considerations apply to the bonds, angles, and torsions in which the pseudo-atom participates. In this kind of united atom representation, one typically eliminates all explicit hydrogen atoms except those that have the capability to participate in hydrogen bonds ("polar hydrogens"). An example of this is the Charmm 19 force-field.

The polar hydrogens are usually retained in the model, because proper treatment of hydrogen bonds requires a reasonably accurate description of the directionality and the electrostatic interactions between the donor and acceptor groups. A hydroxyl group, for example, can be both a hydrogen bond donor and a hydrogen bond acceptor, and it would be impossible to treat this with a single OH pseudo-atom. Note that about half the atoms in a protein or nucleic acid are nonpolar hydrogens, so the use of united atoms can provide a substantial savings in computer time.

Examples of applications

Molecular dynamics is used in many fields of science.

- First macromolecular MD simulation published (1977, Size: 500 atoms, Simulation Time: 9.2 ps=0.0092 ns, Program: CHARMM precursor) Protein: Bovine Pancreatic Trypsin Inhibitor. This is one of the best studied proteins in terms of folding and kinetics. Its simulation published in Nature magazine paved the way for understanding protein motion as essential in function and not just accessory.^[22]
- MD is the standard method to treat collision cascades in the heat spike regime, i.e. the effects that energetic neutron and ion irradiation have on solids and solid surfaces.^{[23] [24]}

The following two biophysical examples are not run-of-the-mill MD simulations. They illustrate notable efforts to produce simulations of a system of very large size (a complete virus) and very long simulation times (500 microseconds):

- MD simulation of the complete satellite tobacco mosaic virus (**STMV**) (2006, Size: 1 million atoms, Simulation time: 50 ns, program: NAMD) This virus is a small, icosahedral plant virus which worsens the symptoms of infection by Tobacco Mosaic Virus (TMV). Molecular dynamics simulations were used to probe the mechanisms of viral assembly. The entire STMV particle consists of 60 identical copies of a single protein that make up the viral capsid (coating), and a 1063 nucleotide single stranded RNA genome. One key finding is that the capsid is very unstable when there is no RNA inside. The simulation would take a single 2006 desktop computer around 35 years to complete. It was thus done in many processors in parallel with continuous communication between them.^[25]
- Folding Simulations of the Villin Headpiece in All-Atom Detail (2006, Size: 20,000 atoms; Simulation time: 500 μ s = 500,000 ns, Program: folding@home) This simulation was run in 200,000 CPU's of participating personal computers around the world. These computers had the folding@home program installed, a large-scale distributed computing effort coordinated by Vijay Pande at Stanford University. The kinetic properties of the Villin Headpiece protein were probed by using many independent, short trajectories run by CPU's without continuous real-time communication. One technique employed was the Pfold value analysis, which measures the probability of folding before unfolding of a specific starting conformation. Pfold gives information about transition state structures and an ordering of conformations along the folding pathway. Each trajectory in a Pfold calculation can be relatively short, but many independent trajectories are needed.^[26]

Molecular dynamics algorithms

Integrators

- Verlet-Stoermer integration
- Runge-Kutta integration
- Beeman's algorithm
- Gear predictor - corrector
- Constraint algorithms (for constrained systems)
- Symplectic integrator

Short-range interaction algorithms

- Cell lists
- Verlet list
- Bonded interactions

Long-range interaction algorithms

- Ewald summation
 - Particle Mesh Ewald (PME)
 - Particle-Particle Particle Mesh P3M
 - Reaction Field Method
-

Parallelization strategies

- Domain decomposition method (Distribution of system data for parallel computing)
- Molecular Dynamics - Parallel Algorithms ^[27]

Major software for MD simulations

- AutoDock suite of automated docking tools,
- Autodock Vina improved local search algorithm, suite of automated docking tools,
- Abalone (classical, implicit water)
- ABINIT (DFT)
- ACEMD ^[28] (running on NVIDIA GPUs: heavily optimized with CUDA)
- ADUN ^[29] (classical, P2P database for simulations)
- AMBER (classical)
- Ascalaph ^[30] (classical, GPU accelerated)
- CASTEP (DFT)
- CPMD (DFT)
- CP2K ^[31] (DFT)
- CHARMM (classical, the pioneer in MD simulation, extensive analysis tools)
- COSMOS ^[32] (classical and hybrid QM/MM, quantum-mechanical atomic charges with BPT)
- Desmond (classical, parallelization with up to thousands of CPU's)
- Culgi ^[33] (classical, OPLS-AA, Dreiding, Nerd, and TraPPE-UA force fields)
- DL_POLY ^[34] (classical)
- ESPResSo (classical, coarse-grained, parallel, extensible)
- Fireball ^[35] (tight-binding DFT)
- GROMACS (classical)
- GROMOS (classical)
- GULP (classical)
- Hippo ^[36] (classical)
- HOOMD-Blue ^[37] (classical, accelerated by NVIDIA GPUs, heavily optimized with CUDA)
- Kalypso ^[38] MD simulation of atomic collisions in solids
- LAMMPS (classical, large-scale with spatial-decomposition of simulation domain for parallelism)
- LPMD ^[39] Las Palmeras Molecular Dynamics: flexible and modular MD.
- MacroModel (classical)
- MACSIMUS ^[40] (classical, polarizability, thread-based parallelization)
- MDynaMix (classical, parallel)
- MOLDY ^[41] (classical, parallel) latest release ^[42]
- Materials Studio ^[43] (Forcite MD using COMPASS, Dreiding, Universal, cvff and pcff forcefields in serial or parallel, QMERA (QM+MD), ONESTEP (DFT), etc.)
- MOSCITO (classical)
- NAMD (classical, parallelization with up to thousands of CPU's)
- nano-Material Simulation Toolkit ^[44]
- NEWTON-X ^[45] (ab initio, surface-hopping dynamics)
- ORAC (classical)
- ProtoMol ^[46] (classical, extensible, includes multigrid electrostatics)
- PWscf (DFT)
- RedMD ^[47] (coarse-grained simulations package on GNU licence)
- S/PHI/nX ^[48] (DFT)

- SIESTA (DFT)
- VASP (DFT)
- TINKER (classical)
- YASARA ^[49] (classical)
- XMD (classical)

Related software

- Avizo - 3d visualization and analysis software.
- BOSS - MC in OPLS
- esra ^[50] - Lightweight molecular modeling and analysis library (Java/Jython/Mathematica).
- Molecular Workbench ^[51] - Interactive molecular simulations on your desktop.
- Packmol ^[52] Package for building starting configurations for MD in an automated fashion.
- Punto ^[53] is a freely available visualisation tool for particle simulations.
- PyMol - Molecular Visualization software written in python.
- Sirius - Molecular modeling, analysis and visualization of MD trajectories.
- VMD - MD simulation trajectories can be visualized and analyzed.

Specialized hardware for MD simulations

- Anton - A specialized, massively parallel supercomputer designed to execute MD simulations.
- MDGRAPE - A special purpose system built for molecular dynamics simulations, especially protein structure prediction.

See also

- Molecule editor
 - Molecular graphics
 - Molecular modeling
 - Computational chemistry
 - Energy drift
 - Force field (chemistry)
 - Force field implementation
 - Monte Carlo method
 - Molecular design software
 - Molecular mechanics
 - Molecular modeling on GPU
 - Protein dynamics
 - Implicit solvation
 - Car-Parrinello method
 - Symplectic numerical integration
 - Software for molecular mechanics modeling
 - List of software for Monte Carlo molecular modeling
 - Dynamical systems
 - Theoretical chemistry
 - Statistical mechanics
 - Quantum chemistry
 - Discrete element method
 - List of nucleic acid simulation software
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- List of molecular graphics systems
- List of web resources for visualizing molecular dynamics

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External links

- The Blue Gene Project (<http://researchweb.watson.ibm.com/bluegene/>) (IBM)JawBreakers.org
- D. E. Shaw Research (<http://deshawresearch.com/>) (D. E. Shaw Research)
- Soft Matter & Molecular Biophysics Group (<http://www.smbb.usc.sitew.com/>)
- Molecular Physics (<http://www.tandf.co.uk/journals/titles/00268976.asp>)
- Statistical mechanics of Nonequilibrium Liquids (<http://www.phys.unsw.edu.au/~gary/book.html>) Lecture Notes on non-equilibrium MD
- Introductory Lecture on Classical Molecular Dynamics (<http://www.fz-juelich.de/nic-series/volume10/sutmann.pdf>) by Dr. Godehard Sutmann, NIC, Forschungszentrum Jülich, Germany
- Introductory Lecture on Ab Initio Molecular Dynamics and Ab Initio Path Integrals (<http://www.fz-juelich.de/nic-series/volume10/tuckerman2.pdf>) by Mark E. Tuckerman, New York University, USA
- Introductory Lecture on Ab initio molecular dynamics: Theory and Implementation (<http://www.fz-juelich.de/nic-series/Volume1/marx.pdf>) by Dominik Marx, Ruhr-Universität Bochum and Jürg Hutter, Universität Zürich
- Online course on (MSE 597G) An Introduction to Molecular Dynamics (<http://nanohub.org/resources/5838>) by Alejandro Strachan
- Lecture Notes on *Short Course on Molecular Dynamics Simulation* Ashlie Martini (2009) (<http://nanohub.org/resources/7570>)

List of web resources for visualizing molecular dynamics

Name	License	Citation	Comments
ANM	free	[1]	computes and visualizes normal modes
Ascalaph Graphics ^[2]	free		visualizes MDynaMix simulations
Database of Macromolecular Movements ^[3]	free	[4]	analyzes protein hinge motions
DSMM ^[5]	free	[6]	movies of MD simulations
Dyneomics ^[7]	free	[8]	interactive visualization of MD trajectories
FIRST/FRODA ^[9]	free	[10]	uses constraints to generate conformational ensembles and trajectories
Force Field Explorer ^[11]	free		graphical interface to TINKER
MoDEL ^[12]	free		deposit and access MD trajectories
Moviemaker ^[13]	free	[14]	generates animations of protein motions
NOMAD-ref ^[15]	free	[16]	compute and visualizes normal modes
Yale Morph Server ^[3]	free	[17]	animations transitions between two states

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List of molecular graphics systems

This is a list of software systems that are used for visualizing macromolecules.

The tables below indicates which types of data can be visualized in each system: **EM** = Electron microscopy; **HM** = Homology modelling; **MD** = Molecular Dynamics; **MM** = Molecular modelling and molecular orbital visualization; **MRI** = Magnetic resonance imaging; **NA** = Nucleic Acids; **NMR** = nuclear magnetic resonance; **Optical** = Optical microscopy; **SMI** = Small molecule interactions; **XRC** = X-ray crystallography data such as electron density.

Stand-alone systems

Name	Data	License	Technology	Citation	Comments
Ascalaph Graphics ^[2]	MM MD	free	C++	[1]	
Avizo	EM MM MRI Optical XRC	commercial ^[2]	Windows, Linux, Mac	[3] [4] [5]	
Avogadro ^[6]	MM XRC MD	free and open-source	C++/Qt, can be extended with Python modules		
BALLView	MM Nucleic Acids XRC SMI	free and open-source, GPL	C++ and Python; Windows, Linux, Solaris, and MacOS X	BALL project ^[7]	BALLView uses OpenGL and the real time ray tracer RTFact as render backends. For both renderers, BALLView offers stereoscopic visualization in several different modes.
Cn3D		free	stand-alone application	[8] [9]	
CheVi ^[10]	SMI	free	stand-alone application		

Coot ^[11]		free		[12]	
Crystal Studio [13]	MM XRC	commercial ^[14]	Windows	[15]	Various Models: Ball & Stick, Stick, Space Filling, Ribbon etc. Plot XRD and Neutron Powder Patterns
Friend ^[16]	MM SA MSA	free	Win, Linux	[17] [18]	Fast, can work with hundreds of structures and thousands of sequences; millions of atoms. Crosstalk between sequence and structure modules. Sequence module based on Jalview. Accurate structural alignment by TOPOFIT method. Also available as applet to interface sequence/structure databases.
Gabedit	XRC MM	free and open-source	C		
gOpenMol [19]	MD MM	free		[20]	
ICM-Browser		free	Windows, Mac, Linux, fast C++ graphics, free plugin and activeICM for Web delivery	[21]	multiple objects, symmetry, 3D wavefront, alignments, chemistry, tables, plots
Jmol		free and open-source	Java applet or stand-alone application	[22]	Supports advanced capabilities such as loading multiple molecules with independent movement, surfaces and molecular orbitals, cavity visualization, crystal symmetry
MDL Chime		free for noncommercial use, proprietary	C++ browser plugin for Windows only	[23]	Calculates molecular surfaces coloured by electrostatic or hydrophobic potential. Originally based on RasMol.
Molden	MM XRC			[24]	
MOE	MM XRC	commercial		Molecular Operating Environment (MOE)	
Molekel	MM XRC	free and open-source	Java3D applet or stand-alone application		
NOCH		free and open-source		[25]	
O		free for noncommercial use		[26]	see also [27]
PyMOL	XRC SMI EM	free for noncommercial use, open-source	Python	[28]	According to the author, almost a quarter of all published images of 3D protein structures in the scientific literature were made using PyMOL.
Qmol ^[29]	MM	free, open-source	C	[30]	Provided by DNASTAR
RasMol		free and open-source	C stand-alone application	[31] [32] [33]	
Sirius		free and open-source	Java3D applet or stand-alone application		

SPARTAN	MM QM	commercial [34]	stand-alone application	[35]	visualize and edit biomolecules, extract bound ligands from PDB files for further computational analysis, full molecular mechanics and quantum chemical calculations package with streamlined graphical user interface.
SRS3D Viewer [36]	HM	free and open-source	Java3D applet or stand-alone application	[37] [38]	Integrates 3D structures with sequence and feature data (domains, SNPs, etc.).
UCSF Chimera	XRC SMI EM MD	free for noncommercial use [39]	Python	[40] [41]	Includes single/multiple sequence viewer, structure-based sequence alignment, automatic sequence-structure crosstalk for integrated analyses. [42]
VMD	EM MD MM	free for noncommercial use [43]	C++	[44] [45]	
WebMol		free	Java applet and stand-alone	[46] [47]	Includes advanced structural analysis features such as packing of secondary structural elements and surface calculations.
WHAT IF	HM XRC	shareware for academics	stand-alone	[48]	Old-fashioned interface; very good software for the experienced bioinformatician; nearly 2000 protein-structure related options; comes with 500 page writeup.
Yasara	HM NMR XRC	commercial; free version for education and elementary structure work	stand-alone	[49]	Very advanced graphics; Best in homology model optimisation in CASP-2008; many drug design options;

Web-based systems

Name	Data	License	Technology	Citation	Comments
Relibase [50]	SMI	partly free (full functionality requires a license)	Java applet integrated into web front-end	[51]	
WebMol		free	Java applet and stand-alone	[46] [47]	Includes advanced structural analysis features such as packing of secondary structural elements and surface calculations.
SRS3D Viewer [36]	HM	free and open-source	Java3D applet or stand-alone application	[37] [38]	Integrates 3D structures with sequence and feature data (domains, SNPs, etc.).

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External links

- Saric, Marc. "Free Molecular Modelling Programs" (http://www.marcsaric.de/index.php/Free_Molecular_Modelling_Programs). A rather detailed, objective, and technical assessment of about 20 tools.
- "PDB list of molecular graphics tools" (http://www.rcsb.org/pdb/static.do?p=software/software_links/molecular_graphics.html).
- "World Index of Molecular Visualization Resources" (<http://www.molvisindex.org>).
- "Molecular Visualization Resources by Eric Martz" (<http://molviz.org>).

Interactomics

Interactomics is a discipline at the intersection of bioinformatics and biology that deals with studying both the interactions and the consequences of those interactions between and among proteins, and other molecules within a cell^[1]. The network of all such interactions is called the Interactome. Interactomics thus aims to compare such networks of interactions (i.e., interactomes) between and within species in order to find how the traits of such networks are either preserved or varied. From a mathematical, or mathematical biology viewpoint an interactome network is a graph or a category representing the most important interactions pertinent to the normal physiological functions of a cell or organism.

Interactomics is an example of "top-down" systems biology, which takes an overhead, as well as overall, view of a biosystem or organism. Large sets of genome-wide and proteomic data are collected, and correlations between different molecules are inferred. From the data new hypotheses are formulated about feedbacks between these molecules. These hypotheses can then be tested by new experiments^[2].

Through the study of the interaction of all of the molecules in a cell the field looks to gain a deeper understanding of genome function and evolution than just examining an individual genome in isolation^[1]. Interactomics goes beyond cellular proteomics in that it not only attempts to characterize the interaction between proteins, but between all molecules in the cell.

Methods of interactomics

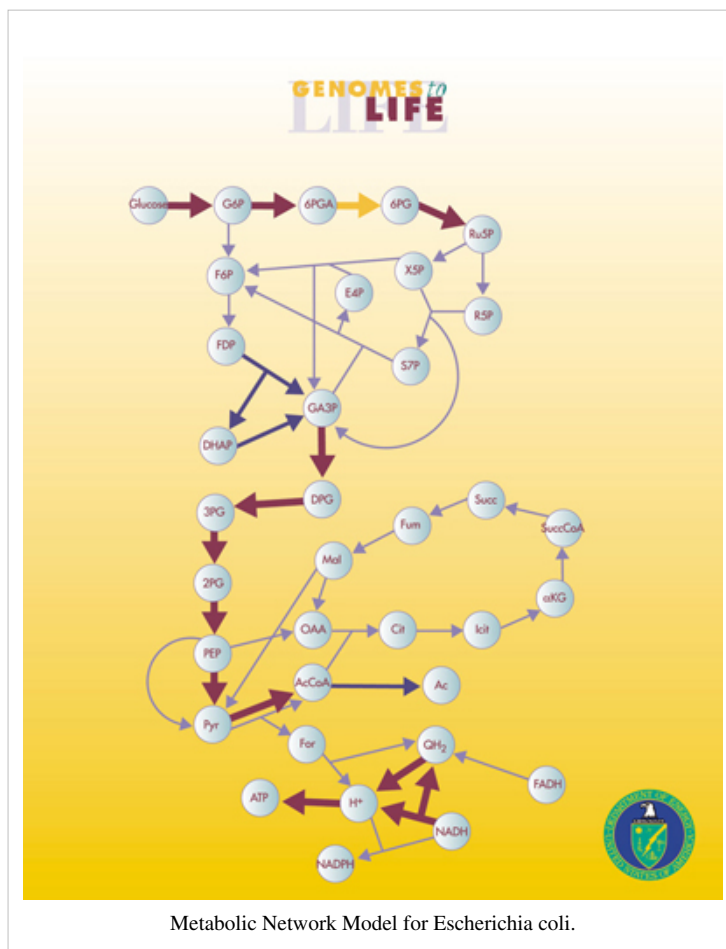
The study of the interactome requires the collection of large amounts of data by way of high throughput experiments. Through these experiments a large number of data points are collected from a single organism under a small number of perturbations^[2] These experiments include:

- Two-hybrid screening
- Tandem Affinity Purification
- X-ray tomography
- Optical fluorescence microscopy

Recent developments

The field of interactomics is currently rapidly expanding and developing. While no biological interactomes have been fully characterized. Over 90% of proteins in *Saccharomyces cerevisiae* have been screened and their interactions characterized, making it the first interactome to be nearly fully specified^[3].

Also there have been recent systematic attempts to explore the human interactome^[1] and^[4].



Other species whose interactomes have been studied in some detail include *Caenorhabditis elegans* and *Drosophila melanogaster*.

Criticisms and concerns

Kiemer and Cesareni^[1] raise the following concerns with the current state of the field:

- The experimental procedures associated with the field are error prone leading to "noisy results". This leads to 30% of all reported interactions being artifacts. In fact, two groups using the same techniques on the same organism found less than 30% interactions in common.
- Techniques may be biased, i.e. the technique determines which interactions are found.
- Interactomes are not nearly complete with perhaps the exception of *S. cerevisiae*.
- While genomes are stable, interactomes may vary between tissues and developmental stages.
- Genomics compares amino acids, and nucleotides which are in a sense unchangeable, but interactomics compares proteins and other molecules which are subject to mutation and evolution.
- It is difficult to match evolutionarily related proteins in distantly related species.

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- [4] further citation needed

External links

- Interactomics.org (<http://interactomics.org>). A dedicated interactomics web site operated under BioLicense.
- Interactome.org (<http://interactome.org>). An interactome wiki site.
- PSIBase (<http://psibase.kobic.re.kr>) Structural Interactome Map of all Proteins.
- Omics.org (<http://omics.org>). An omics portal site that is openfree (under BioLicense)
- Genomics.org (<http://genomics.org>). A Genomics wiki site.
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